ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

РОССИЙСКИЙ КАРДИОЛОГИЧЕСКИЙ ЖУРНАЛ

Russian Journal of Cardiology

SCIENTIFIC, PEER-REVIEWED MEDICAL JOURNAL

RUSSIAN SOCIETY OF CARDIOLOGY

IN ISSUE:

IN FOCUS:

Epidemiology and prevention. Sports cardiology and rehabilitation

№ 5 | 2021

РОССИЙСКОЕ
КАРДИОЛОГИЧЕСКОЕ
ОБЩЕСТВО

Russian Society of Cardiology

Scientific peer-reviewed medical journal

Mass media registration certificate № 017388
dated 06.04.1998

Periodicity — 12 issues per year
Circulation — 7 000 copies

The Journal is in the List of the leading scientific journals and publications of the Supreme Examination Board (VAK)

The Journal is included in Scopus, EBSCO, DOAJ

Russian Citation Index:
SCIENCE INDEX (2019) 2,710
Impact-factor (2019) 1,668

Complete versions of all issues are published:
www.elibrary.ru

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Printed: OneBook, Sam Poligraphist, Ltd.
129090, Moscow, Protopopovsky per., 6.
www.onebook.ru

RUSSIAN JOURNAL OF CARDIOLOGY

№ 26 (5) 2021
founded in 1996

Editorial office:
119049, Moscow,
ul. Shabolovka, 23-254
e-mail: cardiojournal@yandex.ru
Tel. +7 (985) 768 43 18

Publisher:
Silicea-Poligraf
e-mail: cardio.nauka@yandex.ru

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2021-5

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

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MANUSCRIPT PUBLICATION RULES (2019)
http://russjcardiol.elpub.ru/jour/about/submissions#authorGuidelines

Dear colleagues,

We are glad to present you the fifth issue of the Russian Journal of Cardiology for 2021, which describes the problems of epidemiology and prevention of cardiovascular diseases (CVDs), sports cardiology, and cardiac rehabilitation.

The "Original articles" section contains 14 papers. Most of them are devoted to CVD epidemiology in Russia, including the results of the ESSE-RF study. So, the factors associated with carotid plaque burden in the adult general population of Western Siberia were considered. The issue also contains data on the associations of dietary patterns and abdominal obesity in the adult population, as well as on the associations of eating habits and poor nutrition with cardiovascular diseases among the Omsk Oblast population. Also, the prevalence of behavioral and biological risk factors for noncommunicable diseases among rural residents of the Altai Krai was evaluated. The issue describes associations of prehypertension with cardiometabolic and hormonal factors in a population sample of St. Petersburg residents, as well as the relationship of different levels of high-sensitivity C-reactive protein (hs-CRP) with cardiovascular events and assess its contribution to the development of outcomes in Russian regions.

Nadezhda P. Lyamina

The problem of epidemiology is also addressed in works devoted to the associations of psychosocial stress with the social environment, lifestyle and risk factors for cardiovascular diseases in middle-aged male Muscovites, as well as to the age-related trends of physical activity and work capacity among men and women in an open urban population. Of undoubted interest is the comparative analytical study on hypotension and survival in Russian and United States population. The study by Drapkina O. M., et al. describes the regional specifics of changes in mortality rates from acute coronary artery disease in 82 Russian regions. The conformable issues were studied by Samorodskaya I. V. and Semenov V. Yu.

Other articles in this section are devoted to the assessment of predictive potential of cardiovascular risk factors and their associations with arterial stiffness in people of European and Korean ethnic groups, as well as to the comparative analysis of high cardiovascular risk markers and stress echocardiography results depending on the type of blood pressure response to exercise in patients without obstructive coronary artery disease.

The section ends with the paper devoted to the rapid popliteal artery release sensu A. N. Kazantsev in acute thrombosis in patients with COVID-19, which reflects the urgent problem of modern medicine and, in particular, cardiology.

Irina A. Trubacheva

This issue also presents literary reviews on topical problems of prevention and cardiac rehabilitation, the introduction of modern techniques, experience, and knowledge. Modern cardiac rehabilitation requires the introduction of novel management techniques based on a multidisciplinary and physiologically founded approaches in rehabilitation with proven effectiveness.

Rehabilitation of cardiac patients with COVID-19 is of great importance. To date, there is not enough evidence on the medical rehabilitation of cardiac patients with COVID-19 in the world. The following questions remain open: how should medical rehabilitation be managed? What rehabilitation measures are required for COVID-19 survivors? What kind of patients need rehabilitation? The release of the Consensus "Novel coronavirus infectious disease COVID-19: features of comprehensive cardiac and respiratory rehabilitation" is very timely and important, because it presents the opinion of leading experts from five Russian professional communities.

As is customary, the journal presents clinical guidelines of the Russian Society of Cardiology, which were approved by the Ministry of Health of the Russian Federation: "Supraventricular tachycardia in adults" and "Hypertrophic cardiomyopathy".

Key provisions and recommendations for sports for various CVDs are presented in the translated version of the 2020 European Society of Cardiology guidelines on sports cardiology and exercise in patients with CVD, which includes the latest research on training for cardiovascular patients. We hope this document serves as a useful clinical guide as well as a stimulus for future research and new knowledge in sports cardiology.

Best regards, on behalf of the editorial staff
Nadezhda P. Lyamina
Doctor of Medical Science, Professor
Irina A. Trubacheva
Doctor of Medical Science

Russian Journal of Cardiology 2021;26(5):4379
doi:10.15829/1560-4071-2021-4379
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Factors associated with carotid plaque burden in the adult general population

Kaveshnikov V. S., Trubacheva I. A., Serebryakova V. N.

Aim. To study the relationship between carotid plaque burden and conventional, behavioral, and social cardiovascular risk factors.

Material and methods. The object of the study was 469 people (women, 49%) from a representative sample of the general population aged 25-64 years (cross-sectional ESSE-RF study) with the presence of one or more atherosclerotic plaques in the carotid arteries. The study participants underwent cardiac screening and carotid ultrasound. All respondents signed informed consent. The number of involved segments and the average plaque height were studied. The associative analysis included blocks of conventional, social, and behavioral risk factors for cardiovascular diseases. The study of relationships was carried out using linear and log-linear models. An error probability <5% was considered significant.

Results. According to multivariate analysis, age (in men), male sex, smoking, systolic blood pressure (SBP), total cholesterol, heart rate, alcohol abuse, statin and β-blocker therapy were interrelated with the number of involved segments. In turn, the average plaque size was associated with age (in men), male sex, higher education, alcohol abuse, smoking, and high-sensitivity C-reactive protein.

Conclusion. The results obtained confirm the leading role of age (in men), smoking, SBP, total cholesterol, β-blockers as indicators of the number of involved segments. Alcohol abuse and heart rate have shown associations between the ages of 40-50 years and thus may contribute to premature atherosclerosis. Key role of age (in men), sex (among those ≥50 years old), and educational status in average plaque height in this study was confirmed. A significant contribution was also made by alcohol abuse, smoking, high-sensitivity C-reactive protein. The obtained data do not confirm the hypothesis about the contribution of atherogenic lipoproteins and SBP to average plaque height. The study results can be useful for studying the plaque burden role in risk stratification and further development of cardiovascular prevention.

Keywords: population study, ultrasound examination, carotid atherosclerosis, plaque burden, risk factors.

Relationship and Activities: none.

Acknowledgments. The authors are grateful to all participants of the ESSE-RF study (Tomsk) for their invaluable contribution to this work. The authors express their special gratitude to Doctor of Medical Science, Professor T. V. Balakhonova (Moscow) for consulting on the ultrasound measurements; Yu. V. Zhernakova (Moscow) for coordinating the ESSE-RF study, T. I. Kotkina (Moscow) for the determination of high-sensitivity C-reactive protein and lipid profile parameters in the ESSE-RF study.

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Received: 01.03.2021
Revision Received: 22.03.2021
Accepted: 28.03.2021

For citation: Kaveshnikov V. S., Trubacheva I. A., Serebryakova V. N. Factors associated with carotid plaque burden in the adult general population. *Russian Journal of Cardiology*. 2021;26(5):4379. (In Russ.) doi:10.15829/1560-4071-2021-4379

The current trends in cardiovascular diseases (CVD) in Russia and other countries of the world continue to indicate its leading contribution to the premature mortality of the working-age population. In view of the significant socioeconomic damage, CVD prevention by early detection and correction of their risk factors (RFs) is considered as one of the priorities of the long-term socioeconomic development of Russia [1].

Known to date, 50-60% of mortality among population is due to classical RFs of CVD [2]. In various directions, the search for additional RFs continues, which can be influenced or used to develop prognostic tools. The promising tools include peripheral vascular ultrasound [3]. From the early research of carotid stenosis, current papers is increasingly devoted to subclinical atherosclerosis, quantitative assessment and its role in cardiovascular risk stratification. To determine the severity of atherosclerotic involvement, parameters of plaque burden (PB) are used. Research indicates the relationships between such parameters and cardiovascular events [3, 4].

It is known that the development of atherosclerosis and CVD is promoted by major RFs. However, it remains unclear why, with the same susceptibility to major RFs, the individual severity of atherosclerosis varies widely? What additional factors influence the atherogenesis, and to what extent does PB measurement help in predicting cardiovascular risk?

A considerable volume of data on the factors influencing the development and severity of atherosclerosis originates in clinical studies. The extent to which clinical patterns can be extrapolated to the entire population is an important question that can be answered by epidemiological studies. Examples of such studies studying the relationship between PB and RFs are Atherosclerosis Risk in Communities, Malmö Diet and Cancer study, Tromsø Study. In the Russian working-age population, these issues have not been sufficiently studied.

The aim of the current paper was to study the relationships between the key PB indicators in the carotid system and the classical, behavioral and social RFs of CVD in the adult working-age population.

Material and methods

As part of the ESSE-RF cross-sectional study, the analysis of data from 469 respondents aged 25-64 years (n=1600; women, 59%) with one or more atherosclerotic plaques in the carotid system. The detailed design of the study and sampling methods were published earlier [5]. All subjects signed informed consent. All respondents underwent standard cardiac screening and carotid duplex ultrasound using a high-end ultrasound system with a 7,5 MHz linear transducer. The number of involved carotid segments (common and internal carotid arteries, bifurcation) on the right and left, and the maximum plaque height in each segment were measured. The average plaque height was determined as the sum of plaque sizes in 6 segments divided by the number of involved segments. The number of involved segments and the average plaque height were analyzed. Details of ultrasonic measurements are given in previously published works [6, 7].

The association analysis included age, sex, education, marital status, number of children, income level, type of dwelling; the presence of hypertension, myocardial infarction, stroke, diabetes in first-degree relatives; physical activity, smoking, alcohol consumption; glomerular filtration rate, diabetes; medical appointment in the past year, body mass index, systolic and diastolic blood pressure, heart rate (HR); taking beta-blockers (BB), diuretics, angiotensin-converting enzyme inhibitors, statins; total cholesterol (TC), high density lipoproteins (HDL), triglycerides, highly sensitive C-reactive protein (hs-CRP), glucose.

The boundary between moderate alcohol consumption and abuse was considered to be 168 g of ethanol per week for men and 84 g for women. Intense physical activity was considered an exercise for at least 20-30 minutes, causing the sweating or mild shortness of breath. Glomerular filtration rate was determined using the CKD-EPI equation.

Statistical analysis was performed using SPSS (v.13) and R (v.2.15) programs. Frequencies were compared by the chi-squared method and Fisher's exact test. To compare quantitative variables, Student's t and the Mann-Whitney test were used. To analyze the number of involved segments and the average plaque height, a generalized linear model of the gamma family of distributions with a log link function and a log-linear model were used, respectively. The variables such as sex, age, income level, and statin intake were entered into the model as covariates. An error probability <5% was considered significant.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committees of all participating centers approved this study. All patients signed informed consent.

Results

Comparative characteristics of the surveyed sample depending on sex are presented in Table 1. Women were on average 2 years older than men, smoked less often, had lower number of involved

Table 1

Comparative characteristics of the surveyed sample

Factor	Men (n=239)	Women (n=230)	p
Age, years, m(se)	54,2 (0,46)	56,2 (0,41)	0,001
Sex, %	51,0	49,0	-
Higher education, %	44,6	38,3	0,164
Smoking ⩾10 cigarettes per day, %	42,9	10,0	<0,001
Cardiovascular diseases, %	20,4	20,0	0,910
Statins, %	6,3	7,8	0,501
Number of plaques, m(se)	2,03 (0,07)	1,57 (0,06)	<0,001
Average plaque height, m(se)	1,96 (0,04)	1,71 (0,03)	<0,001
SBP, mm Hg	144,4 (1,43)	140,4 (1,52)	0,054
Total cholesterol, mmol/L	5,9 (0,09)	6,4 (0,09)	<0,001
Glucose, mmol/L	5,8 (0,10)	5,9 (0,11)	0,450

Abbreviation: SBP — systolic blood pressure.

segments, average plaque height and a higher level of TC.

To identify the factors associated with the number of involved segments, a multiple stepwise regression model was created (χ^2=184,0; df=14, p<0,001) with the inclusion of significant interactions — (male) sex with age (b=0,037; p<0,001) and systolic blood pressure (SBP) (b=-0,009; p<0,001), age with alcohol abuse (b=-0,030; p=0,008) and heart rate (b=-0,008; p=0,014). The results are shown in Table 2.

As can be seen from the table, age is associated with the number of involved segments only in men, and the SBP level — only in women, respectively. Regular smoking of 10 or more cigarettes a day, TC showed a direct association, while BB intake — an inverse association, respectively. The sex effect varied depending on age and SBP. With an average SBP and an adjustment for other RFs, significant sex differences were revealed only for patents aged ⩾60 years.

A significant contribution to the studied parameter was made by alcohol abuse and heart rate. Such associations were limited in age to 50 and 55 years, respectively.

To study the factors interrelated with the average plaque height, a multiple stepwise regression model (F=9,85; df=10, p<0,001; R^2=0,18) was created with the inclusion of significant interactions — age with the (male) sex (b=0,008; p=0,014) and alcohol abuse (b=-0,012; p=0,042), respectively. The results are shown in Table 3.

Age in men, smoking 10 or more cigarettes a day, hs-CRP, and alcohol abuse under the age of 55 were associated with higher average plaque height. The contribution of alcohol abuse to the studied parameter was higher in the young age than in the middle one. Higher education has been shown to be the only protective factor. After adjusting for significant covariates, the sex difference in the average plaque height was observed already at the age of 50, and it increased further.

Discussion

The development of approaches to improving the cardiovascular health of the population requires not only knowledge of RFs associated with cardiovascular morbidity and mortality, but also a more substantive understanding of the relationship between factors and structural vascular defects.

Measurement of peripheral arterial plaque burden is possible using such integral parameters as the total plaque height. However, to study various atherogenesis aspects, it is advisable to separately consider the number of involved segments and the average plaque height, reflecting the extent of atherosclerosis and the average severity of atheromatosis, respectively. The aim of this work was to study plaque burden patterns from this point of view.

Evidence from epidemiological studies on the plaque burden determinants is controversial. In most of them, the role of major RFs is described — age, male sex, TC, HDL, smoking, SBP, etc. [8-11].

In this study, age (in men) and smoking made the greatest contribution to this indicator, which is consistent with other papers [8-10]. In women, the relationship with age was not noted, which confirms the results of univariate analysis [6]. It should be noted the weak effect of sex on the of involved segments, observed only in persons aged ⩾60 years.

Table 2

Factors associated with the number of involved segments according to multivariate analysis

Factor	Coefficient	t-test	p
Age* (men)	0,034	6,589	<0,001
Age* (women)	-0,003	-0,663	0,507
Male sex* :			
— age of 50 years	-0,017	0,109	0,914
— age of 55 years	0,169	1,080	0,280
— age of 60 years	0,355	2,138	0,033
SBP (men)	-0,001	-1,040	0,298
SBP (women)	0,008	6,452	<0,001
Regular smoking ⩾10 cigarettes	0,315	6,422	<0,001
Total cholesterol	0,049	3,177	0,001
Alcohol abuse:			
— age of 40 years	0,418	2,545	0,011
— age of 45 years	0,270	2,267	0,023
— age of 50 years	0,122	1,439	0,150
Heart rate			
— age of 45 years	0,099	2,481	0,013
— age of 50 years	0,057	2,118	0,034
— age of 55 years	0,016	0,812	0,417
Beta blockers	-0,137	-2,162	0,031
Statins	0,263	3,099	0,002
Income status	0,019	0,866	0,375

Note: * — mean values of other factors.
Abbreviation: SBP — systolic blood pressure.

A strong association with the studied parameter is demonstrated by SBP in women. The important role of this factor is noted in most works [8-11]. In a population study performed in Japan, age and SBP were the only determinants of plaque number in women [8]. The absence of such effect in men is inconsistent with research data, which requires further study.

Atherogenic lipoproteins are considered key factors in atherogenesis. In this study, TC showed a significant association with the number of involved segments, which confirms the data of previous works [8-10] and indirectly indicates its effect on the formation of new plaques ABP. This talking point is confirmed in the prospective study by Johnsen SH, et al. [12], demonstrating the relationship of TC with the formation of new plaques.

The analysis shows a direct association of heart rate and alcohol abuse with the number of involved segments among people aged 40-50 years. The influence of these factors has been less often discussed in population studies. It has been reported that there is a relationship between resting heart rate and the occurrence of plaques in the Chinese population [13]. The results obtained indirectly confirm the prospective study by Kiechl S, et al. [14], demonstrating the association of alcohol abuse with the involvement of new carotid segments in the northern Italian population.

An inverse association of the studied parameter with BB intake was revealed. One of the reasons of this effect may be the achievement of lower heart rate among older people, in whom the prescription rate of these drugs increases. Antihypertensive therapy, as well as individual antihypertensive drugs of other classes did not show significant relationships in this aspect.

The most significant predictors in average plaque height were age (in men), male sex among people aged ⩾50 years, and higher education. In contrast to the number of involved segments, the sex effect was observed 10 years earlier. The epidemiological studies on the effect of sex in this aspect are very ambiguous, while foreign studies showed less significant sex differences [8-10]. The education influence on plaque burden was rarely studied in

Table 3

Factors associated with the average plaque height according to multivariate analysis

Factor	Coefficient	t-test	p
Age (men)	0,112	4,847	<0,001
Age (women)	0,003	1,278	0,201
Male sex:			
— age of 45 years	0,029	0,673	0,501
— age of 50 years	0,070	2,265	0,024
— age of 55 years	0,111	4,394	<0,001
Statins	0,082	1,828	0,068
Income status	0,003	0,278	0,781
Higher education	-0,078	-3,244	0,001
Regular smoking ⩾10 cigarettes	0,068	2,408	0,016
C-reactive protein (log)	0,024	2,406	0,017
Alcohol abuse:			
— age of 45 years	0,183	2,762	0,006
— age of 50 years	0,120	2,544	0,011
— age of 55 years	0,057	1,339	0,181

foreign publications. The data obtained indicate the protective effect of higher education on plaque burden.

Alcohol abuse, regular smoking of 10 or more cigarettes and hs-CRP were associated with higher average plaque height. Compared to the number of involved segments, the effect of alcohol abuse in this regard covered a wider age segment and up to 50 years was at least as important or more significant than smoking. The relationship between the studied parameter and hs-CRP confirms the role of chronic inflammation in the atheroma progression.

There was no significant associations of average plaque sizes with lipid profile parameters. TC is the leading modifiable factor effecting carotid plaque formation in the general population [15]. TC can be associated with the number of involved segments in men [8], the severity of maximal stenosis [10], and the total plaque height [8]. There is a relationship between the total plaque area and low density lipoproteins to HDL ratio [9]. In prospective studies, the relationship of TC with the total plaque area progression is confirmed in the study by Header M, et al. [16] and refuted by Johnsen SH, et al. [12]. The association of the factor with the average plaque height indirectly indicates the contribution of this factor to plaque burden progression due to the increase in plaque size. In most of the above papers, however, authors studied associations in relation to the total plaque burden, which does not allow us to fully determine the influence of RF on its individual components. Thus, the results obtained are consistent with other papers demonstrating the leading role of atherogenic lipoproteins in plaque burden progression due to the formation of new atherosclerotic plaques.

Study limitations include its cross-sectional design, which does not give a complete picture of the cause-and-effect relationship. The assumptions made are probabilistic in nature. The revealed relationships with TC, SBP, heart rate, alcohol abuse require further study, including as part of prospective studies.

Conclusion

The results obtained confirm the leading role of age (in men), smoking, SBP and total cholesterol as indicators of the number of involved segments. Alcohol abuse and heart rate have shown associations between the ages of 40-50 years and thus may contribute to premature atherosclerosis. Key role of age (in men), sex (among those ⩾50 years old), and educational status in average plaque height in this study was confirmed. A significant contribution was also made by alcohol abuse, smoking, high-sensitivity C-reactive protein. The obtained data do not confirm the hypothesis about the contribution of atherogenic lipoproteins and SBP to average plaque height. The study results can be useful for studying the plaque burden role in risk stratification and further development of cardiovascular prevention.

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Relationships and Activities: none.

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Russian Journal of Cardiology 2021;26(5):4230
doi:10.15829/1560-4071-2021-4230
https://russjcardiol.elpub.ru

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Predictive potential of cardiovascular risk factors and their associations with arterial stiffness in people of European and Korean ethnic groups

Brodskaya T. A.[1], Nevzorova V. A.[1], Shahgeldyan K. I.[2,3], Geltser B. I.[2], Vrazhnov D. A.[4,5], Kistenev Yu. V.[5,6]

Aim. To compare the effect of cardiovascular risk factors on aortic stiffness in people of European and East Asian ethnic groups.

Material and methods. A total of 266 patients aged 18-60 years of European (n=133) and Korean (n=133) ethnic groups were examined. Clinical assessment was carried, Also, following blood parameters was evaluated: total cholesterol (TC), low- (LDL-C) and high- (HDL-C) density lipoprotein cholesterol, apolipoproteins A (apo-A) and B (apo-B), triglycerides (TG), uric acid, creatinine, glucose, adiponectin, resistin. The aortic pulse wave velocity (PWV) and central blood pressure (CBP) were determined using a Tensiomed arteriograph (Hungary). The study design included 3 stages. The first stage included statistical analysis using Mann-Whitney, χ^2, Fisher tests, while the second one – determination of weighing coefficients of individual risk factors on aortic PWV. The third stage consists of verification of the relationship between ethnicity and aortic PWV using multivariate logistic regression and stochastic gradient boosting (SGB).

Results. In Europeans, the median values of growth, body mass index (BMI), waist circumference (WC) and waist-to-height ratio were significantly higher, while the levels of apo-B, TC, HDL-C, LDL-C, TG was significantly lower than in Asians. Koreans had higher blood concentrations of UA, creatinine, glucose, while the resistin concentration was 1,8 times lower. Among Europeans, the odds ratio of developing hypertension (HTN) was significantly higher. The level of aortic PWV in people of different ethnic groups did not differ significantly. Univariate logistic regression showed a dominant influence of age, CPP and waist-to-height ratio on aortic PWV. A less noticeable significant relationship with aortic PWV had HTN, female sex, BMI, levels of systolic, diastolic and pulse BP. Multivariate logistic regression and SGB showed the maximum prediction accuracy when 5 predictors were combined in one model: age, height, HTN, LDL-C, and ethnicity. Comparable accuracy was demonstrated by a model where glucose level was used instead of LDL-C. The results indicate a nonlinear relationship between the ethnic factor and aortic PWV. Its predictive potential was realized only in combination with functional and metabolic status parameters of patients. In Koreans, the threshold values of these factors can be significantly higher than in Europeans.

Conclusion. Developed using modern machine learning technologies, the assessment aortic PWV models taking into account the ethnic factor can be a useful tool for processing and analyzing data in predictive studies.

Keywords: cardiovascular risk, ethnicity, aortic stiffness, machine learning, mathematical models.

Relationships and Activities. This work was supported by RFBR grants № 19-29-01077 and 18-29-03131.

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Received: 09.12.2020
Revision Received: 07.01.2021
Accepted: 03.02.2021

For citation: Brodskaya T. A., Nevzorova V. A., Shahgeldyan K. I., Geltser B. I., Vrazhnov D. A., Kistenev Yu. V. Predictive potential of cardiovascular risk factors and their associations with arterial stiffness in people of European and Korean ethnic groups. *Russian Journal of Cardiology*. 2021;26(5):4230. (In Russ.) doi:10.15829/1560-4071-2021-4230

According to the World Health Organization, cardiovascular diseases continue to be the leading cause of disability and premature mortality of the population, even in the context of a coronavirus disease 2019 (COVID-19) pandemic [1, 2]. It is known that the majority of cardiovascular events are associated with cardiovascular remodelling, the subclinical manifestations of which remain undiagnosed for many years. Currently, the issues of cardiovascular risk (CVR) personification and its prognostic assessment are relevant [3]. An important but insufficiently studied aspect of this approach is phenotypic and genetic characteristics of specific individuals, including their ethnicity [3-5]. The data obtained indicate that the traditional CVR factors in different ethnic groups have their own specifics [6]. In the context of current demographic situation when various ethnic groups are not fully tied to their habitats, the issues of ethnicity-related personified CVR assessment acquire special relevance. European and American experts have developed adjustment factor or additional points to the traditionally used CVR scores in first-generation immigrants living in the European Union and the United States [7, 8]. There is available data from specific studies indicating differences in the implementation of traditional risk factors (RFs), most often, hypertension (HTN), in individuals of different ethnic groups living in the Russian Federation [5, 9]. The effect of RF sum is reflected in the target organ damage, which in the early, preclinical stages can be described by some markers, among which excessive aortic stiffness occupies a special place [10, 11]. Increased stiffness of the aorta and large arteries is one of the integral vascular remodelling indicators, which determines the development of vascular events, including in young people [7, 8, 10]. At the same time, the use of arterial stiffness as the only predictor of CVR models based on logistic regression (LR) showed insufficient predictive value. As a number of studies shows, the use of modern machine learning (ML) technologies makes it possible to increase the efficiency of predicting adverse cardiovascular events.

The aim was to compare the effect of cardiovascular risk factors on aortic stiffness in people of European and East Asian ethnic groups.

Material and methods

The study involved 266 people (men, 130; women, 136) aged 18-60, living in the Primorsky Krai and the Sakhalin Oblast. The first group included 133 subjects (mean age, 40,3 years; 95% confidence interval (CI) [38,6; 42]) of European (Slavic) ethnicity, and the second — 133 subjects (mean age, 40,1 years; 95% CI [38,9; 41,1]) of East Asian (Korean) ethnicity (second and third-generation immigrants). The study included patients followed up in outpatient clinics, which signed informed consent. The exclusion criteria were age over 60 years, obesity, symptomatic HTN, arrhythmias, acute disease, and exacerbated chronic disease. The study design was approved by the interdisciplinary ethics committee of the Pacific State Medical University (Vladivostok, Russia). All patients signed written informed consent. The study protocol included 61 characteristics obtained using anthropometric, clinical, and investigational examination methods. All patients were measured for height, body weight, waist circumference (WC), and body mass index (BMI). The study took into account data on sex, smoking status, HTN, and family history. There were following laboratory parameters characterizing the clinical and metabolic status of subjects: total cholesterol (TC), high- and low-density lipoprotein cholesterol (HDL-C and LDL-C), apolipoprotein A (apoA), apolipoprotein B (apoB), uric acid (UA), triglycerides (TG), C-reactive protein (CRP), glucose, adiponectin, and resistin. Arterial stiffness parameters were determined by non-invasive angiography (TensioClinic TL1, TensioMed, Hungary). We also studied aortic pulse wave velocity (APWV), systolic (SBP) and diastolic (DBP) blood pressure on the radial artery, pulse pressure (PP), central aortic blood pressure (CAP), and heart rate. APWV was considered as a continuous or categorical dichotomous (APWV >10 m/s corresponds to an increased level) dependent variable. The input traits were a subgroup of potential predictors and were presented as continuous and categorical variables. Methods of statistical analysis and ML were used for data processing and analysis. The first ones included

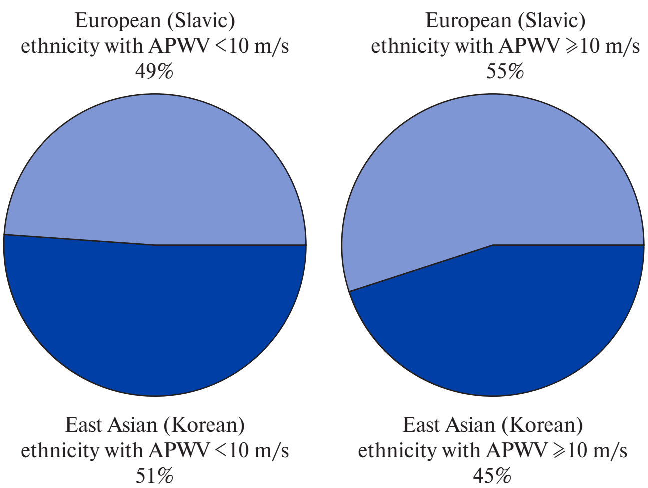

Figure 1. The ratio of persons from different ethnic groups with normal and increased arterial stiffness.
Abbreviation: APWV — aortic pulse wave velocity.

Table 1

Clinical, anthropometric, functional, and metabolic parameters in individuals of different ethnic groups

Parameter	Europeans, n=133	Koreans, n=133	OR, 95% CI	p-value
Age, years	42 [39; 44]	40 [39; 42]		0,75
Male sex, n	64 (48,9%)	66 (51,1%)	0,81 [0,5; 1,3]	0,46
Height, cm	173 [170; 176]	166 [164; 170]		<0,00001
Weight, kg	80 [75; 85]	68 [64; 74]		<0,00001
BMI, CU	26,4 [25,5; 27,8]	24,6 [23,5; 26]		0,00041
WC, cm	89 [85; 93]	82 [80; 86]		0,00018
WHtR, CU	51,7 [49,1; 53,6]	50 [47,9; 51,1]		0,037
UA, mmol/L	0,34 [0,32; 0,41]	0,43 [0,39; 0,55]		0,00024
apoA, g/l	1,8 [1,58; 1,96]	1,6 [1,53; 1,73]		0,15
apoB, g/l	0,85 [0,79; 0,9]	1,075 [0,97; 1,16]		<0,00001
LDL-C, mmol/L	3,57 [3,27; 3,89]	3,925 [3,63; 4,26]		0,037
HDL-C, mmol/L	1,22 [1,11; 1,34]	1,395 [1,24; 1,69]		0,0032
TG, mmol/L	1,45 [1,19; 1,61]	1,77 [1,5; 2,1]		0,026
Total cholesterol, mmol/L	5,47 [5,06; 5,83]	6,34 [6,06; 6,65]		<0,00001
Creatinine, μmol/L	74,45 [70,4; 77,7]	99,6 [91; 107,2]		<0,00001
CRP, mg/L	0,945 [0,67; 1,56]	1,6 [1,2; 2,3]		0,126
Glucose, mmol/L	5,13 [5; 5,23]	6,67 [6,44; 7,15]		<0,00001
Resistin, pg/ml	5,1 [5; 5,3]	2,8 [2,5; 3,7]		0,000054
Adiponectin, pg/ml	5,8 [5,36; 6]	5,08 [3,55; 6,5]		0,43
HTN, n (%)	74 (55,6%)	42 (31,6%)	2,7 [1,6; 4,5]	0,000127
SBP, mm Hg	132 [129; 136]	124 [120; 130]		0,0026
DBP, mm Hg	80 [77; 83]	77 [75; 80]		0,136
CAP, mm Hg	120,6 [115,3; 125]	115,4 [110,25; 122,7]		0,5
PP, mm Hg	51 [39; 53]	45 [43; 47]		0,00054
Heart rate, bpm	71 [68; 72]	71 [70; 72]		0,7
APWV (continuous), m/s	7,69 [7,45; 8,15]	7,55 [7,17; 8,05]		0,43
APWV ⩾10, n (%)	27 (20,3%)	22 (16,5%)	1,3 [0,7; 2,4]	0,53

Note: OR was calculated only for categorical factors.

Abbreviations: HTN — hypertension, apoA — apolipoprotein A, apoB — apolipoprotein B, DBP — diastolic blood pressure, CI — confidence interval, BMI — body mass index, UA — uric acid, OR — odds ratio, WC — waist circumference, TC — total cholesterol, PP — pulse pressure, SBP — systolic blood pressure, APWV — aortic pulse wave velocity, CRP — C-reactive protein, TG — triglycerides, HDL-C — high-density lipoprotein cholesterol, LDL-C — cholesterol low density lipoproteins, CAP — central aortic pressure, HR — heart rate.

descriptive statistics (median (Me), 95% CI), Spearman correlation analysis, Chi-squared, Fisher, Mann-Whitney tests, and univariate weighted LR. The second ones involved following ML techniques: multivariate LR, stochastic gradient boosting (SGB). Statistical significance was confirmed by a p-value <0,05. The development of multivariate LR models was carried out using only one of the correlated variables in their structure to eliminate the multicollinearity. The accuracy of the models was assessed by three quality metrics: area under the ROC curve, sensitivity, and specificity. The models were developed on a training sample (3/4 patients) and verified on a test sample (1/4). Cross-validation was performed with averaging quality metrics at least 100 times over randomly selected data. When developing the LR and SGB models, the Korean ethnicity was coded "1", and the European one — "0".

The study design included 3 phases. At the first, statistical analysis was used, with the help of which intergroup comparisons were carried out. For continuous variables, the Mann-Whitney test was used, since a preliminary assessment of distribution normality by the Shapiro-Wilk test showed a negative result. The chi-square test was used to compare categorical variables, and Fisher's exact test — to assess the odds ratio (OR) with a 95% CI. Comparisons were made for groups with different ethnicity (Europeans and Koreans), as well as for subjects with normal and

Table 2

Assessment of the effect of CVR factors on APWV in the general population

Parameter	APWV <10 m/s, n=217	APWV ≥10 m/s, n=49	OR, 95% CI	p-value
Age	39 [38; 41]	47 [45; 47]		<0,0001
Male sex	129 (59,4%)	14 (28,5%)		
Female sex	88 (40,6%)	35 (71,4%)	3,6 [1,9; 7,4]	0,00017
Height	171,5 [170; 173]	164 [163; 167]		0,00017
WC	84 [82; 87]	89,5 [82; 95]		0,24
BMI	25,36	26,15		0,034
WHtR	50 [48,8; 51,1]	52,4 [49,1; 57,4]		0,012
UA	0,39 [0,36; 0,43]	0,34 [0,31; 0,46]		0,53
ApoA	1,7 [1,59; 1,77]	1,64 [1,21; 2,34]		0,76
ApoB	0,92 [0,86; 0,97]	0,92 [0,68; 0,98]		0,54
LDL-C	3,79 [3,42; 3,99]	3,55 [3; 4,37]		0,69
HDL-C	1,28 [1,2; 1,41]	1,26 [0,95; 1,52]		0,21
TG	1,6 [1,42; 1,74]	1,4 [1,1; 2,67]		0,83
Cholesterol	5,92 [5,61; 6,17]	5,55 [4,9; 6,21]		0,12
Creatinine	83,4 [77,4; 90,1]	74,9 [68,7; 89]		0,1
CRB	1,12 [0,91; 1,6]	2,6 [0,42; 7,97]		0,11
Glucose	5,625 [5,44; 5,82]	5 [4,9; 6,2]		0,064
Resistin	4,7 [3,9; 5]	4,78 [2,25; 5,5]		0,88
Adiponectin	5,7 [5,3; 6]	5,68 [4,7; 6,4]		0,79
HTN	77 (35,5%)	39 (79,6%)	7 [3,4; 15,6]	<0,0001
SPB	128 [123; 131]	138 [126; 145]		0,014
DBP	77 [76; 80]	83 [79; 90]		0,01
PP	47 [46; 50]	51 [47; 58]		0,04
CAP	116,2 [111,8; 120,2]	136,5 [121; 155,4]		0,00016
Heart rate	71 [70; 72]	70 [68; 72]		0,24

Abbreviations: HTN — hypertension, apoA — apolipoprotein A, apoB — apolipoprotein B, DBP — diastolic blood pressure, CI — confidence interval, BMI — body mass index, UA — uric acid, OR — odds ratio, WC — waist circumference, TC — total cholesterol, PP — pulse pressure, SBP — systolic blood pressure, APWV — aortic pulse wave velocity, CRP — C-reactive protein, TG — triglycerides, HDL-C — high-density lipoprotein cholesterol, LDL-C — cholesterol low density lipoproteins, CAP — central aortic pressure, HR — heart rate.

increased APWV. At the second phase, according to normalized characteristics, using univariate LR, weights were determined that corresponded to the significance of effect of specific CVR factors on APWV in the general population and in ethnic groups. At the third phase, multivariate models based on LR and SGB were developed, the structure of which was step by step supplemented with potential predictors of increased arterial stiffness. With an increase in the quality metrics, the factor was considered as a predictor of vascular remodelling. Data processing and analysis were performed in R in the R-studio environment and in Python using the XGBoost and TensorFlow packages.

Results

At the first phase, we analyzed possible differences in demographic, anthropometric, clinical, and investigational parameters between the two ethnic groups (Table 1).

It was found that ethnic groups did not significantly differ in age and sex composition. The median values of anthropometric parameters (height, weight, BMI, WC and waist-to-height ratio (WHtR)) were significantly higher in Europeans. In this group, such lipid profile parameters as apoB, TC, HDL-C, LDL-C, TGs were significantly lower than in the comparison group. The Koreans had a higher blood concentration of UA, creatinine, glucose, while the resistin level was 1,8 times lower than in Europeans. At the same time, CRP and adiponectin levels in the comparison groups did not differ. HTN with a higher SBP and PP levels was significantly more common in the European group. Compared to Koreans, Europeans had a significantly higher risk of HTN (OR, 2,7 [1,6; 4,5]) (Table 1). At

Table 3

Weighting coefficients of univariate LR models for assessing APWV in the general population

Predictive factor	Weighting coefficient	p-value
Age	6,1	<0,0001
Ethnic group	-0,25	0,43
Female sex	1,3	0,00017
Height	-3,4	0,0007
BMI	2,18	0,013
WHtR	3	0,0046
HTN	2	<0,0001
SBP	2,4	0,0055
DBP	2,1	0,016
PP	1,4	0,055
CAP	4,3	<0,0001
Creatinine	-2,4	0,11
GFR	0,32	0,89
Glucose	-2,8	0,28
UA	-0,82	0,66
HDL-C	-1,7	0,16
LDL-C	-0,67	0,6
TC	-0,34	0,077

Note: (-) — inverse dependence of APWV on this factor.

Abbreviations: HTN — hypertension, DBP — diastolic blood pressure, BMI — body mass index, UA — uric acid, WC — waist circumference, TC — total cholesterol, PP — pulse pressure, SBP — systolic blood pressure, GFR — glomerular filtration rate, APWV — aortic pulse wave velocity, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, CAP — central aortic pressure.

Table 4

Weighting coefficients of univariate LR models in assessing the predictive potential of CVR factors in European and Korean ethnic groups

Predictive factor	Europeans		Koreans	
	Weighting coefficient	p-value	Weighting coefficient	p-value
Age	6	0,00002	4,1	0,0018
Female sex	1,2	0,0087	1,6	0,006
Height	-4,87	0,00073	-2,2	0,043
BMI	2,6	0,023	0,65	0,5
WHtR	2,9	0,023	1,33	0,22
HTN	2,68	0,00043	1,65	0,0008
SBP	2,4	0,0055	3	0,00003
DBP	2,1	0,016	3,7	<0,00001
PP	1,4	0,055	0,85	0,25
CAP	4,3	0,00003	5	<0,00001
LDL-C	0,04	0,8	0,06	0,9

Abbreviations: HTN — hypertension, DBP — diastolic blood pressure, BMI — body mass index, WC — waist circumference, PP — pulse pressure, SBP — systolic blood pressure, LDL-C — low-density lipoprotein cholesterol, CAP — central aortic pressure.

the same time, the APWV in individuals of different ethnic groups did not differ significantly (OR, 0,78 [0,41; 1,46], p=0,53) (Figure 1).

Analysis of RF effect on the increase in APWV was carried out for dichotomous variable (Table 2). The results of comparing CVR among the general

Table 5

Quality of multivariate LR and SGB models for predicting APWV in the general population

№	Predictive factor	Logistic regression			Stochastic gradient boosting		
		AUC	Sensitivity, %	Specificity, %	AUC	Sensitivity, %	Specificity, %
1	Age	0,763±0,06	74,4±11	67,2±7	77,3±6	73,1±11	67,2±8
2	Age + female sex	0,802±0,06	67,8±14	72±7	79,6±6	70,5±15	69,4±9
3	Age + female sex + ethnicity	0,796±0,06	67,5±13	71,9±7	79,3±6	69,5±15	69,5±9
4	Age + height	0,787±0,06	75,6±10	68,4±6	0,794±0,06	70,2±11	70,6±7
5	Age + height + ethnicity	0,778±0,06	72,8±11	70,1±6	0,792±0,06	68,8±11	70,4±7
6	Age + height + female sex	0,793±0,06	68,9±12	70,7±6	0,796±0,06	69,3±0,12	71±7
7	Age + height + female sex + ethnicity	0,786±0,06	68,5±12	71,2±6	0,792±0,06	68,5±12	71,2±7
8	Age + height + CAP	0,804±0,09	73,6±17	80,9±7	0,757±0,08	63,7±16	79,4±7
9	Age + height + HTN	0,827±0,06	77,4±11	73,4±6	0,82±0,06	78,8±11	72,2±6
10	Age + height + HTN + ethnicity	0,823±0,06	77,3±11	74,1±6	0,817±0,06	78,1±12	72,4±6
11	Age + height + HTN + LDL-C	0,833±0,09	78,8±17	75±9	0,785±0,09	76±16	74,6±10
12	Age + height + HTN + LDL-C + ethnicity	0,867±0,08	80,3±13	85,5±7	0,843±0,08	81,2±15	76,8±7
13	Age + height + HTN + glucose	0,818±0,09	79±16	72,9±9	0,809±0,09	74,6±19	73,9±8
14	Age + Height + HTN + glucose + ethnicity	0,857±0,08	86,4±14	78,4±8	0,846±0,09	80,7±17	76±8

Note: the averaged quality metrics values were obtained on test samples.

Abbreviations: HTN — hypertension, LDL-C — low-density lipoprotein cholesterol, CAP — central aortic pressure, AUC — area under the ROC curve.

population with APWV <10 m/s and APWV ⩾10 m/s showed that aortic stiffness increase is significantly associated only with age, female sex (OR, 3,6 [1,9; 7,4], p=0,00017), anthropometric parameters (height, BMI, WHtR), HTN (OR, 7 [3,4; 15,6], p<0,0001), the level of SBP, DBP, PP and CAP.

To verify the possible interrelationships of CVR factors with aortic stiffness, based on univariate LR, we constructed models for assessing APWV with the calculation of weighting coefficients that allow us to clarify the predictive value of potential predictors. This approach significantly expands the potential of processing and analyzing data due to a more detailed classification of CVR factors' effect on the resulting variable (Table 3).

Evaluation of the weighting coefficients of univariate regression models made it possible to identify CVR factors that had significant relationships with APWV. The age (6,1), CAP (4,3), and WHtR (3) had a direct dominant effect on APWV. An intense inverse relationship was recorded between the height of subjects and arterial stiffness (-3,4). Factors such as HTN, female sex, SBP, DBP, PP, and BMI had a less pronounced, but reliable direct relationship with APWV. At the same time, the effect of ethnicity and metabolic parameters on arterial stiffness was not significant.

For a more accurate assessment of ethnicity-APWV relationships, we have developed univariate LR models separately for each ethnic group (Table 4).

The analysis of weighting coefficients in the comparison groups showed that anthropometric parameters (WHtR and BMI) have a significant effect on APWV only in the European population. In this group of subjects, the dependence of arterial stiffness on age, height, and HTN was more noticeable. Among Koreans, sex (female), as well as SBP and DBP had a more intense relationship with APWV.

At the next phase, we developed multivariate LR and SGB models and performed their cross-validation on 100 random samples. The main quality metrics was obtained: area under the ROC curve, sensitivity and specificity (Table 5).

It was found that in all the models developed, the age of subjects was used as the basic predictor, the high predictive potential of which was also proved at the previous phases (Tables 2-4). The step-by-step inclusion of additional factors in their structure with the subsequent validation of models on test samples showed that the most accurate of them are models 12 and 14, which included the ethnic factor. Analysis of models 1-9 showed that age, female sex, height, CAP and HTN are "self-sufficient" predictors of

Table 6

Weighting coefficients of multivariate LR models with the ethnicity inclusion

Predictive factor	Weighting coefficient/p-value		
Parameter	Model 10	Model 12	Model 14
Age	0,085/0,00056	0,104/0,047	0,084/0,037
Height	-0,073/0,00017	-0,043/0,05	-0,057/0,04
HTN	1,38/0,00005	1,8/0,0065	1,6/0,011
Ethnicity	-0,206/0,44	-3,3/0,016	-3,38/0,011
LDL-C	-	0,168/0,6	-
Glucose	-	-	0,07/0,21

Note: during analysis, Koreans were coded 1, Europeans — 0.
Abbreviations: HTN — hypertension, LDL-C — low-density lipoprotein cholesterol.

arterial stiffness and do not depend on ethnicity. This conclusion was made based on quality metrics obtained for different types of models (LR and SGB), the accuracy of which increased when height or sex were included in their structure and did not change significantly when these factors were combined with ethnicity (models 1-7). It should be noted that sex and height have comparable predictive value, and their combination in one model increases the predictive quality. The presence of HTN was more significant than the CAP, but they both increased the prediction accuracy “without the help” of ethnicity (models 8-9). The maximum rise in quality metrics was recorded when 5 predictors were combined: age, height, HTN, LDL-C, and ethnicity (model 12). Comparable accuracy was demonstrated by a model in which the LDL-C was replaced by serum glucose (model 14). The data obtained indicate a nonlinear relationship between the ethnic factor and APWV. Its predictive potential was realized only when combined with functional and metabolic status parameters of the subjects.

For a more detailed assessment of influence vector of the ethnicity on APWV, we analyzed the weighting coefficients of the models with ethnic factor (Table 6).

Negative weighting coefficients for the selected ethnicity coding (models 12, 14) indicate that an increase in the serum concentration of glucose and LDL_C in Europeans is a RF of increased arterial stiffness. At the same time, among Koreans, these factors were not associated with the risk of increased APWV. It can be assumed that in this cohort of subjects, the realization of pathogenic potential of CVR factors is carried out at their higher threshold values (Table 1).

Discussion

The level of CVR in practice is most often assessed using integral scales. At the same time, the prognostic significance of classical scales and other systems for CVR stratification actively discussed [3, 12, 13]. Most experts note the need to search for novel biological markers that would make it possible to personalize the CVR assessment in an earlier age patients. Of particular interest are the approaches associated with integral CVR parameters, which reflect the RF sum effect on the organism throughout life, including the phenotypic and genetic characteristics of a person. Markers of cardiovascular remodelling and, first of all, parameters of aortic and large arterial stiffness occupy an important place in CVR reclassification. Parameters of arterial or aortic stiffness are recognized as independent predictors of all-cause and cardiovascular mortality, even more significant than CVR factors such as blood pressure or blood cholesterol [10, 11]. An increase in aortic stiffness due to impaired elasticity is considered one of the manifestations of natural aging in humans and CVR escalation [11]. In recent years, research has been intensified using ML to develop prognostic models that assess the CVR [14, 15]. At the same time, there are not enough works on assessing the ethnicity influence on the integral CVR indicators, despite the fact that ethnicity is recognized as a promising factor in CVR reclassification [3, 13].

In the present study, using the developed models, we obtained new data on the probability of CVR factor realization in individuals of the European and Korean ethnic groups. According to our data, the median APWV values in these cohorts did not differ significantly with each other. However, the analysis of weighting coefficients of univariate LR models revealed differences in influence of individual CVR factors on arterial stiffness. Models based on LR and SGB made it possible to verify the high predictive potential of age, female sex, height, HTN and CAP for assessing increased arterial stiffness regardless of ethnicity. Also, the fact that the patient had HTN was more significant than the CAP level, but both of these factors increased the accuracy of the prognosis. At the same time, according to our data, the serum levels of LDL-C and glucose demonstrated predictive value for vascular remodelling only in conjunction with ethnicity, which was confirmed by modelling.

Study limitations. The study limitations includes the inadequate sample size and the need to expand the methods for processing and analyzing data, including using artificial neural networks.

Conclusion

Currently, the topical direction of preventive cardiology is the improvement and adaptation of the well-known CVR stratification scores with the studying novel predictors, including ethnicity [3, 4, 12]. At the same time, it should be noted that for a full revision of classical scales, data are still insufficient, and therefore it is necessary to perform studies with a larger number of representatives of different ethnicity. The data obtained in this study on the influence of individual RFs and their combinations on the risk of increased arterial stiffness in individuals of the European and East Asian races complement the already known information. The analysis indicate that the threshold values of metabolic factors (LDL-C and glucose) associated with increased arterial stiffness in Koreans, compared with the Europeans, may be significantly higher. This hypothesis was confirmed by comparing biochemical parameters in the comparison groups and modelling the aortic stiffness level with stepwise inclusion of potential predictors.

Relationships and Activities. This work was supported by RFBR grants № 19-29-01077 and 18-29-03131.

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Russian Journal of Cardiology 2021;26(5):4365
doi:10.15829/1560-4071-2021-4365
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Hypotension and survival: diagnostic criteria in Russian and United States population

Vilkov V. G., Balanova Yu. A., Kapustina A. V., Muromtseva G. A., Shalnova S. A.

Aim. Based on Russian and United States population studies, to determine the criterion for distinguishing between normal and low blood pressure (BP), which is the most significant for predicting all-cause mortality.

Material and methods. We used data from prospective Russian studies of 14730 men aged 19-82 years (9307 deaths per 342309 person-years of follow-up) and 6141 women aged 18-72 years (2101 deaths per 158727 person-years of follow-up), and two United States population studies: the First National Health and Nutrition Examination Survey (NHANES I) in conjunction with the NHANES I Epidemiologic Followup Study, and the Second National Health and Nutrition Examination Survey (NHANES II) in conjunction with the NHANES II Mortality Study. The total American cohort included only white subjects: 8618 men aged 25-75 years (3130 deaths per 121794 person-years of follow-up) and 11135 women 25-75 years (2465 deaths per 176676 person-years of follow-up). Primary examinations were carried out in 1971-1982, while the latest information on the subjects' survival status was obtained in 2017 (Russia) and 1992 (USA). Kaplan-Meier curves and Cox proportional hazards models were created; all-cause death was taken into account as an outcome.

Results. Survival analysis using Cox models, in which, in addition to BP levels, sex, age and risk factors were taken into account, showed that in persons with a pronounced BP decrease, survival is worse in comparison with those with normal BP. Mean dynamic BP, unfavorable for all-cause mortality, was below 70 and 68 mm Hg and 76 and 72 mm Hg in men and women in the Russian and US cohorts, respectively.

Conclusion. Not only hypertension, but also severe hypotension is associated with increased all-cause mortality compared to normal BP. Survival decrease is manifested in severe hypotension, subject to sex and adjustment for age and risk factors.

Keywords: hypotension, population study, prospective observation, survival, Cox regression.

Relationships and Activities. The work was carried out within the state assignment to the National Medical Research Center for Therapy and Preventive Medicine "Risk factors of NCDs, their significance for predicting the health of the population of different age groups in some regions of the Russian Federation. Assessment of the effect on morbidity and mortality (population study)". Registration number: AAAA-A20-120013090086-0.

Acknowledgments. The authors are grateful to all participants of the ESSE-RF study. This work was made possible by the free access to data from the NHANES series provided by the National Center for Health Statistics (NCHS), USA. Responsibility for the results of analysis, interpretation and conclusion lies with the article authors, while responsibility of NCHS is limited to primary data.

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Received: 26.02.2021
Revision Received: 05.03.2021
Accepted: 28.03.2021

For citation: Vilkov V. G., Balanova Yu. A., Kapustina A. V., Muromtseva G. A., Shalnova S. A. Hypotension and survival: diagnostic criteria in Russian and United States population. *Russian Journal of Cardiology*. 2021;26(5):4365. (In Russ.) doi:10.15829/1560-4071-2021-4365

Hypotension (HoTN) is a condition, the main manifestation of which is an excessive blood pressure (BP) decrease. According to the International Classification of Diseases, Tenth Revision (ICD-10), an excessive BP decrease is considered to be more than 20% of the norm.

The problem of HoTN has received much less attention in comparison with hypertension (HTN), HoTN has always been "in the shadow of HTN" [1]. This is understandable, since HTN is one of the most widespread cardiovascular diseases and at the same time a significant risk factor (RF) for noncommunicable diseases [2], while the HoTN prevalence is much less [3]. However, there is evidence that the dependence of mortality on BP is not steadily increasing, but U-shaped (more precisely, J-shaped), i.e. at an excessively low BP, mortality is higher in comparison with its normal level [4, 5]. However, the severity of this effect is inferior to the increase in HTN-related mortality.

There is no single approach to HoTN diagnosis: some researchers took into account only the BP level; according to another point of view, in addition to BP values, clinical manifestations of insufficient blood supply should be taken into account with the separation of HoTN in physiological and pathological [6].

The BP values, which are regarded as diagnostically significant for HoTN, vary even more. Thus, some foreign researchers consider HoTN in men as systolic blood pressure (SBP) of 110 or diastolic blood pressure (DBP) of 60 mm Hg, as well as in women — SBP of 100 or DBP of 60 mm Hg, regardless of age [7]. In Russia, the most common classification proposed by N.S. Molchanov in the 60s of the XX century, people aged ⩽25 years with SBP <100 or DBP <60 mm Hg were attributed to HoTN, and those aged >25 years with SBP <105 or DBP <60 mm Hg, regardless of sex [6].

At one time, there were disputes regarding the BP thresholds, the excess of which is considered an HTN. These thresholds were determined after the accumulation of data from prospective studies that allowed to study the relationship between BP values and cardiovascular outcomes, including mortality [8].

In this study, we used a similar approach to determine the HoTN criteria, unfavorable for survival.

The aim was to determine, based on Russian and United States population studies, the criterion for distinguishing between normal and low BP, which is the most significant for predicting all-cause mortality

Material and methods

The work used data from Russian prospective studies performed at the National Medical Research Center for Therapy and Preventive Medicine [9] and 2 US population-based studies: the First National Health and Nutrition Examination Survey (NHANES I) together with NHANES I Epidemiologic Followup Study, as well as the Second National Health and Nutrition Examination Survey (NHANES II) together with NHANES II Mortality Study. The studies were carried out in accordance with the Declaration of Helsinki principles.

In this work, we used data from a Russian cohort of 14730 men aged 19-82 years (9307 deaths per 342309 person-years of follow-up) and 6141 women aged 18-72 years (2101 deaths per 158727 person-years of follow-up).

For comparison, we used data from the combined American cohort (only white people): 8618 men aged 25-75 years (3130 deaths per 121794 person-years of follow-up) and 11135 women aged 25-75 years (2465 deaths per 176676 person-years of follow-up).

Primary examinations were carried out in 1971-1982, while the latest data on participants was obtained in 2017 (Russia) and 1992 (USA).

We analyzed age, sex, smoking status, total cholesterol (TC), SBP, DBP, heart rate (HR), body mass index (BMI). According to SBP and DBP values using the Hickam formula, the average dynamic BP (ADBP) was calculated.

For survival analysis, Kaplan-Meier curves [10] and Cox proportional hazards model [11] were created. All-cause death was taken into account as an outcome.

By creating Kaplan-Meier curves, survival was compared in hypo-, normo-, and hypertensive patients. To differentiate hypo- and normotensive persons, several criteria were used [6, 7, 12]; for each criterion, a separate analysis was performed. The criteria of Molchanov N.S. (1962) [6] and Pemberton J (1989) [7] are described in the introduction; according to Chefranova Zh. Yu. (2008) criterion [12], persons aged <35 years with SBP/DBP not higher than 100/60 mm Hg, those aged 36-54 years with SBP/DBP of no more than 110/70 mm Hg, and those aged >54 years with SBP/DBP of no more than 120/70 mm Hg were classified as HoTN. In all cases, HTN included persons with SBP and/or DBP more than or equal to 140 and/or 90 mm Hg.

To develop an original criterion for HoTN, several computational experiments was carried out studying 8 types of thresholds between groups of people with HoTN and normal BP based on ADBP: 68, 70, 72, 74, 76, 78, 80, 82 mm Hg (types I, II, III, IV, V, VI, VII, VIII, respectively). The lower ADBP limit in persons with normal BP was determined in accordance with one of above types, while the upper limit was 100 mm Hg; in persons with high normal

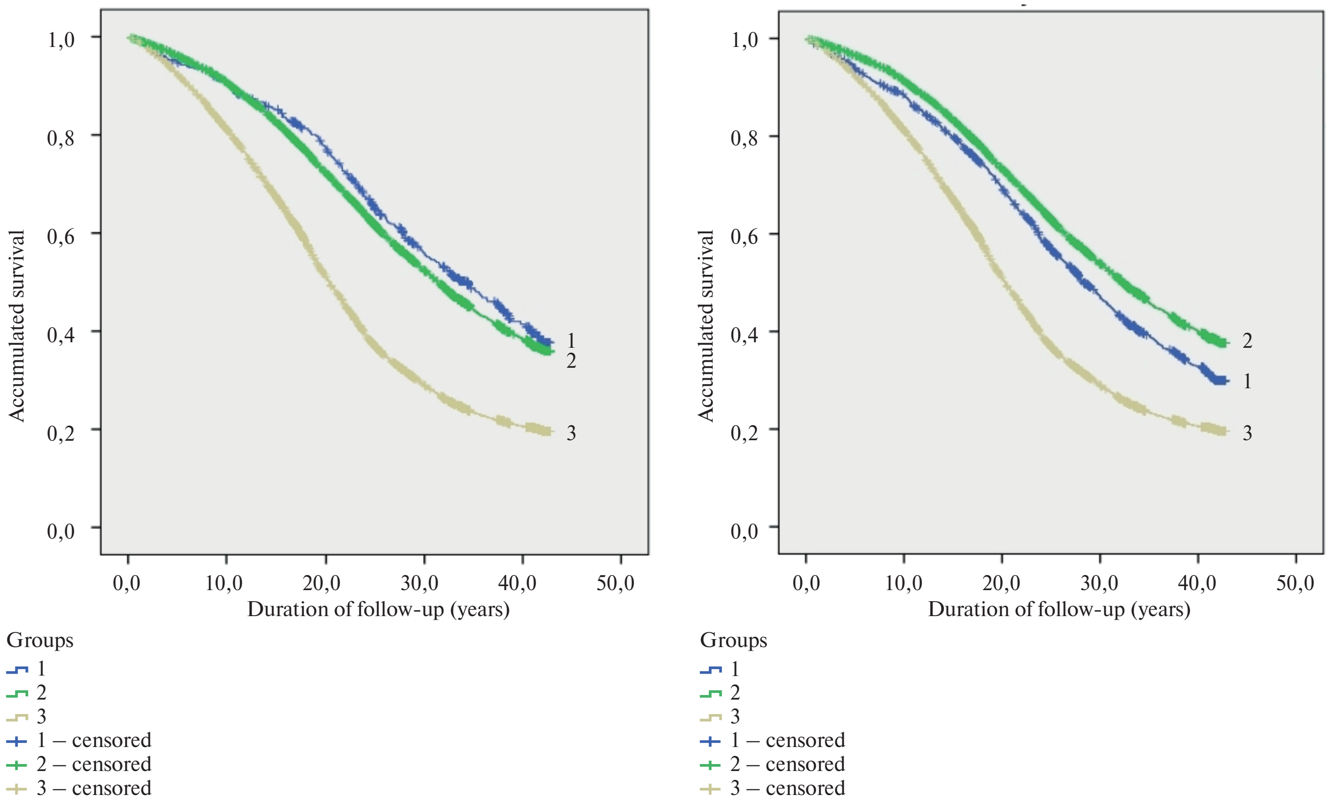

Figure 1. Kaplan-Meier curves in Russian men according to two HoTN criteria: on the left — Molchanov N. S. (1962) [6]; on the right — Chefranova Zh. Yu. (2008) [12].
Groups: 1 — hypertensive patients, 2 — normotensive people, 3 — hypertensive patients.

BP, the boundaries of ADBP were 100-106,7 mm Hg. To differentiate the HTN grades, we used ADBP values, equivalent to the corresponding SBP and DBP values [13]: the group of patients with grade 1-2 HTN included persons with ADBP 106,7-133,3 mm Hg, while grade 3 HTN consisted of those with ADBP >133,3 mm Hg. Cox proportional hazards models were created with independent variables including age, smoking status, HR, BMI, TC, and a categorical variable characterizing the level of ADBP. This variable had values from 1 to 5, which coded belonging to the group of people with HoTN, normal BP, high normal BP, grade 1-2 HTN, grade 3 HTN, respectively. Cox models were created for each of the eight threshold types separately for men and women, for the Russian cohort and the combined cohort from the US population. The models had the same independent variables (see above) and differed in regression coefficient values.

Results

The study of survival in HoTN persons in comparison with normo- and hypertension showed that the results differ significantly depending on the chosen criterion for HoTN [6, 7, 12]. In some cases, the survival curve for HoTN is higher in comparison with normotension, while according to some criteria, the ratio is reversed. Figure 1 shows as examples the survival curves for Russian men using Molchanov N. S. (1962) [6] and Chefranova Zh. Yu. (2008) [12] criterions, which demonstrated the above differences. For all of the above criteria, the differences in survival in persons with hypo- and normotension were relatively small.

The next step was to study survival in individuals with different BP, taking into account sex, age, and RFs. In this work, this was implemented by constructing Cox proportional hazards models separately for men and women. We used independent variables included age, smoking status, TC, BMI and HR values at the initial examination, as well as a categorical variable characterizing belonging to groups of HoTN, normal BP, high normal BP, grade 1-2 HTN, grade 3 HTN. Survival curves were created separately for each of the 5 values of above categorical variable.

We revealed a clear pattern — the lower the borderline ADBP between hypo- and normotension,

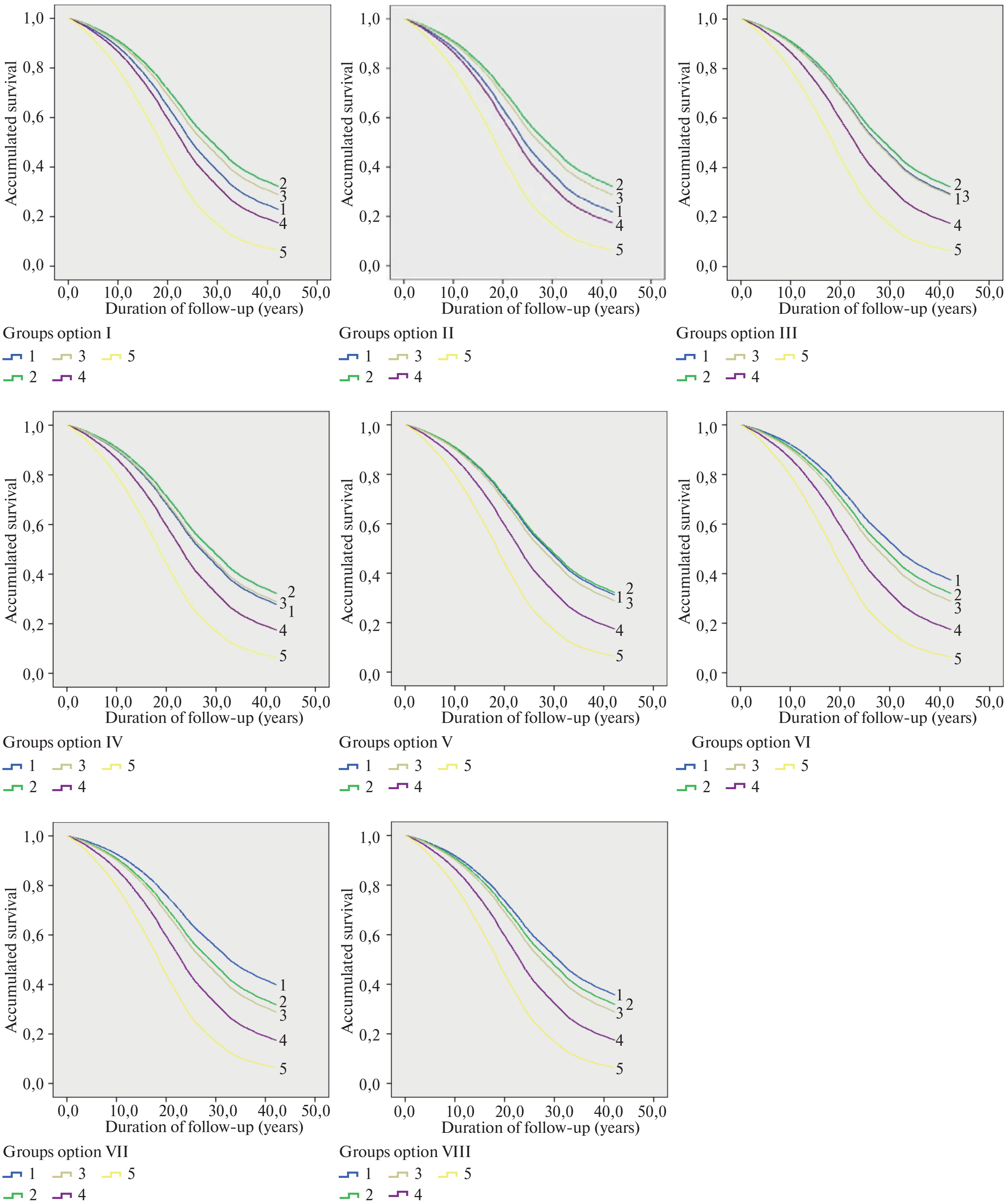

Figure 2. Survival curves estimated using Cox models in Russian men. The models adjusted for age, smoking status, HR, BMI, TC, as well as a categorical variable characterizing belonging to the hypo-, normo- or hypertension groups.
Groups: 1 — HoTN (one of the types I-VIII, the ADBP is less than 68, 70, 72, 74, 76, 78, 80 or 82 mm Hg), 2 — normal BP, 3 — high normal BP, 4 — grade 1-2 HTN, 5 — grade 3 HTN.

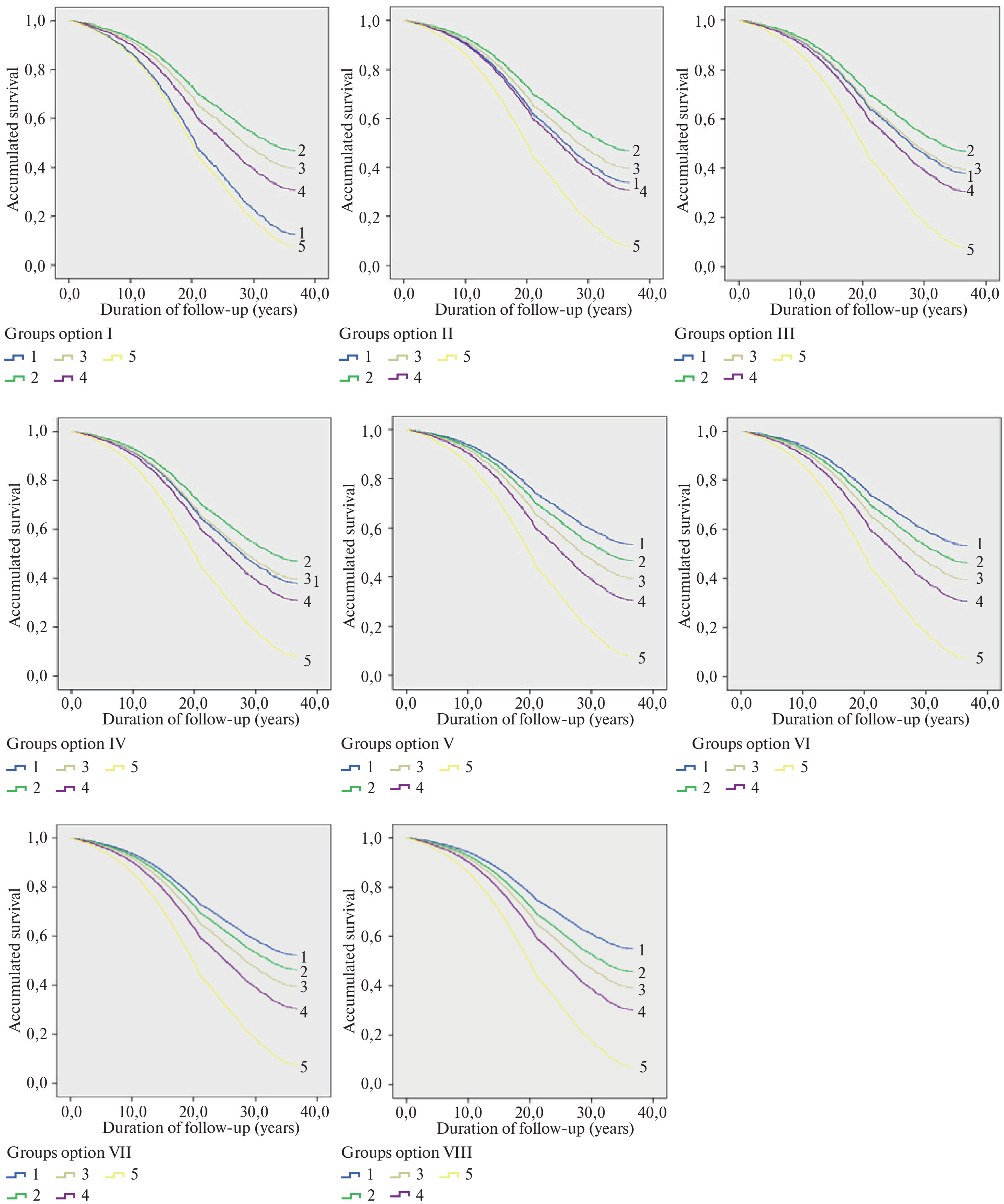

Figure 3. Survival curves estimated using Cox models in Russian women. The models adjusted for age, smoking status, HR, BMI, TC, as well as a categorical variable characterizing belonging to the hypo-, normo- or hypertension groups.
Groups: 1 — HoTN (one of the types I-VIII, the ADBP is less than 68, 70, 72, 74, 76, 78, 80 or 82 mm Hg), 2 — normal BP, 3 — high normal BP, 4 — grade 1-2 HTN, 5 — grade 3 HTN.

the worse the survival of hypotensive patients in comparison with normotensive ones. In each studied cohort, for men and women, the ADBP values were determined, which as a HoTN criterion, shows the worst survival in comparison with normotensive patients.

For example, Figure 2 shows survival curves estimated using Cox models in Russian men for above types of thresholds (I-VIII).

Figure 2 shows that for Russian men, the most unfavorable HoTN is with an ADBP of 70 mm Hg. With the shift of HoTN border to higher ADBP values, the survival curves of hypotensive and normotensive patients converge. Starting with type VI, the survival rate in hypotensive patients becomes better than in normotensive ones.

Figure 3 presents the results for Russian women, which demonstrates that they have the most unfavorable HoTN with an ADBP of 68 mm Hg (type I). As in men, as the threshold of ADBP increases, survival rate in HoTN compared to normotensive patients improves.

Similar computational experiments were carried out in the US cohort. The patterns are the same, but there are only quantitative differences. The thresholds of unfavorable HoTN were 76 and 72 mm Hg in men and women, respectively.

According to Cox models, differences in survival rate between unfavorable HoTN and normotension in the Russian and American cohorts using unweighted values do not formally reach significance due to the small cohort of hypotensive patients (Russian cohort, 24 men and 25 women; US cohort, 78 and 108, respectively). Similar Cox models were created after weighing with a single scaling factor of 10, while the differences between the selected HoTN types with normotensive people in all the cases described above become significant (p<0,02 or less).

Discussion

The HoTN criteria described in the literature in most cases were developed based on the clinical studies without prospective follow-up; the authors focused mainly on the clinical manifestations of inadequate blood supply to organs [6, 7, 12].

There are much fewer publications on the HoTN effect on survival rate and related conclusions are contradictory.

So, according to Robbins JM, et al. (1982) [14], low BP was associated with a decrease in cardiovascular mortality, and therefore HoTN was defined as a non-disease. The prospective study of Leiden (Netherlands) residents after adjustment for sex, age and basic health parameters showed no significant increase in the relative risk of all-cause death in people with low SBP or DBP [4]. According to Lapin V.V. (2008), the incidence of cardiovascular events in persons with stable HoTN does not differ from people with normal BP [15].

On the other hand, the prospective study of 1,5 thousand residents of Ohasama (Japan) aged 40 years and older with a follow-up of 6 years demonstrated an increased death risk not only with an increase, but also with a decrease in BP <119/64 mm Hg [5]. The latest large-scale studies of antihypertensive drugs have shown that SBP <120 mm Hg or DBP <70 mm Hg are associated with an increased risk of cardiovascular events and death [16]. The Russian cohort study of people aged 55 years and older adjusted for RFs revealed an association of cardiovascular mortality with both high BP and SBP <120 mm Hg [17].

The BP values, diagnostically relevant for HoTN, proposed by different researchers vary greatly. For example, the meta-analysis of papers for 1914-1955 considered the HoTN thresholds of SBP from 90 to 120 mm Hg and DBP from 40 to 70 mm Hg [6].

As a theoretical rationale for HoTN threshold, a BP value is proposed, which ensures the maintenance of cerebral flow autoregulation, which is about 70 mm Hg for SBP or 90/60 mm Hg for SBP/DBP [15].

Possible mechanisms of the negative effect of HoTN on survival rate are considered impaired cerebral circulation and autoregulation, neurohumoral dysregulation of BP, and the development of vascular (hypotonic) encephalopathy [18].

Thus, the question of the specific BP value, which distinguishes normo- and hypotension, negatively associated with survival, remains unclear.

We carried out the above computational experiments, using the ADBP values from 68 to 82 mm Hg as the boundary between normo- and hypotension with a step of 2 mm Hg. It turned out that, with adjustment for sex, age, smoking status, heart rate, BMI, TC, there is a range of low BP values associated with a deterioration in survival compared with normotensive patients. In the Russian population, with a 40-year follow-up, the survival rate is worse in men and women with an ADBP of 70 and 68 mm Hg, respectively. These observations were confirmed in the US population with a 20-year follow-up, where decrease in survival rate was observed in men and women with ADBP <76 and 72 mm Hg, respectively.

Identical patterns obtained from the three cohorts from populations of two different countries demonstrates the non-randomness of data obtained.

Study limitations. The problem of HoTN was actively studied in the first third of the 20th century. Then there was a renewed interest due to a sharp increase in its prevalence due to World War II. Due to the small number of modern publications, there are deviations from the journal requirements — some of the papers were published more than 10 years ago.

Conclusion

1. The relationship between BP and survival is not linear. Not only hypertension, but also severe HoTN are associated with an increase in all-cause mortality in comparison with normal BP.

2. The more stringent the HoTN criterion is used (the lower the threshold between hypo- and normotensiion), the worse the survival of hypotensive patients in comparison with normotensive ones.

3. Survival decrease is manifested only in case of severe hypotension — according to the 40-year prospective follow-up in the Russian population, an ADBP of 70 and 68 mm Hg in men and women, respectively.

4. The patterns were confirmed by 20-year prospective follow-up of the US population with an ADBP of 76 and mm Hg in men and women, respectively.

5. These patterns are manifested only with adjustment for sex, age and RFs, in particular, smoking status, HR, BMI, and TC.

Acknowledgments. The authors are grateful to all participants of the ESSE-RF study. This work was made possible by the free access to data from the NHANES series provided by the National Center for Health Statistics (NCHS), USA. Responsibility for the results of analysis, interpretation and conclusion lies with the article authors, while responsibility of NCHS is limited to primary data.

Relationships and Activities. The work was carried out within the state assignment to the National Medical Research Center for Therapy and Preventive Medicine "Risk factors of NCDs, their significance for predicting the health of the population of different age groups in some regions of the Russian Federation. Assessment of the effect on morbidity and mortality (population study)". Registration number: AAAA-A20-120013090086-0.

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Russian Journal of Cardiology 2021;26(5):4363
doi:10.15829/1560-4071-2021-4363
https://russjcardiol.elpub.ru

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Associations of dietary patterns and abdominal obesity in the adult population. Results of the Russian epidemiological ESSE-RF study

Karamnova N. S., Shalnova S. A., Rytova A. I., Shvabskaya O. B., Makarova Yu. K., Balanova Yu. A., Evstifeeva S. E., Imaeva A. E., Kapustina A. V., Muromtseva G. A., Maksimov S. A., Yarovaya E. B., Drapkina O. M.

Abdominal obesity (AO) is an alimentary-dependent risk factor, the development and prognosis of which is directly specified by eating habits.

Aim. To study the associations of dietary patterns and AO among the adult Russian population.

Material and methods. The analysis was carried out using representative samples of male and female population aged 25-64 years (n=19297; men, 7342; women, 11955) from 13 Russian regions. The response was about 80%. Nutrition was assessed based on the prevalence of consumption of the main food groups forming the daily diet. Results are presented as odds ratios and 95% confidence intervals.

Results. Men with AO, compared with men without AO, more often consume red meat and vegetables/fruits daily by 12% and 13%, respectively, as well as less often eat cereals and pasta, confectionery, sour cream, and cottage cheese by 17%, 24%, 14%, and 19%, respectively. In women with AO, compared to women without AO, there are more differences in the diet, as they more often daily consume red meat by 28%, fish and seafood by 26%, poultry by 23%, meat and sausages and fruits/vegetables by 14%, milk, kefir, yogurt by 11%, as well as less often — cereals and pasta, sweets, and sour cream by 11%, 14%, and 8%, respectively. In women with AO, the prevalence and amount of drinking beer and dry wines is lower, but they consume spirits more frequently (p=0,0001), but without significant differences in amount. Men with AO have a higher prevalence and amount of drinking dry and fortified wines, as well as strong alcoholic drinks. Men with AO drinks higher amount of beer. In addition, men with AO showed a positive association with alcohol consumption (χ=53,64, p<0,0001), while women with AO had a negative association (χ=28,64, p<0,0001). Cardioprotective eating habits are more often (17%) present among people with AO without sex differences.

Conclusion. The study revealed significant differences in dietary patterns of persons with AO compared with those without AO, most pronounced in women.

Keywords: dietary patterns, dietary structure, abdominal obesity, obesity, eating habits, diet, alimentary-dependent risk factors.

Relationships and Activities: none.

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Received: 26.02.2021
Revision Received: 10.03.2021
Accepted: 14.03.2021

For citation: Karamnova N. S., Shalnova S. A., Rytova A. I., Shvabskaya O. B., Makarova Yu. K., Balanova Yu. A., Evstifeeva S. E., Imaeva A. E., Kapustina A. V., Muromtseva G. A., Maksimov S. A., Yarovaya E. B., Drapkina O. M. Associations of dietary patterns and abdominal obesity in the adult population. Results of the Russian epidemiological ESSE-RF study. *Russian Journal of Cardiology*. 2021;26(5):4363. (In Russ.) doi:10.15829/1560-4071-2021-4363

Obesity is a significant global problem, rapidly growing in modern society and becoming an epidemic [1]. In Russia, according to the ESSE-RF large-scale epidemiological study, the prevalence of general obesity is 30,8% among women and 26,9% among men, while abdominal obesity (AO) — 38,4% and 24,3%, respectively [2]. Over the decade of 2003-2013, the obesity rate among women increased by 30%, and among men — 2,5 times [2]. The increase in obesity is noted both among the urban and rural population, which, given the difference in physical activity, indicates the increasing role of inadequate nutrition in obesity development. AO is a nutrition-dependent risk factor, the development and prognosis of which is directly determined by the diet. AO is a key risk factor for metabolic syndrome, forming a whole cluster of metabolic disorders and increasing the adverse effect on the patient prognosis.

The study of associations between nutrition and obesity is becoming extremely relevant and in demand for the development of preventive programs. The performed analysis of associations is carried out both with nutritional models [3, 4], characteristics of energy and nutritional status [5-8], and with individual food groups, covering both products from the daily diet (dairy products, fruits and vegetables, meat, etc.) [9-18] and banquet products (confectionery, sugary drinks, processed products) [19]. The interest of researchers is attracted by the contribution of obesity of both raw products [9, 14, 20] and products of various processing degrees [6, 10-12, 19, 21], and regarding dairy products — the fat content [13].

At the moment, the numerous studies in this area are a topic for active scientific discussion, since they are multidirectional in nature and have significant differences depending on the dietary structure in the population.

The aim was to study the associations of dietary patterns and AO among the adult Russian population.

Material and methods

The material was representative samples of male and female population aged 25-64 years (n=22217; men, 8519; women, 13698) from 13 Russian regions (Voronezh, Ivanovo, Volgograd, Vologda, Kemerovo, and Tyumen Oblasts; Republic of North Ossetia-Alania, Krasnoyarsk Krai; Samara, Orenburg, Vladivostok, Tomsk and St. Petersburg), examined as part of the ESSE-RF multicenter epidemiological study. The study was approved by the National Medical Research Center for Therapy and Preventive Medicine, Russian Cardiology Research and Production Complex, Almazov National Medical Research Center, and all other participating centers. All subjects signed an informed consent. The response rate was ~80% [22].

To assess nutrition and dietary habits, a standard questionnaire was used on consumption of the main food groups (red meat, poultry, fish and seafood, sausages and meat delicacies, pickles, cereals and pasta, raw vegetables and fruits, legumes, confectionery and sweets, dairy products: milk, kefir, yoghurt, sour cream/cream, cottage cheese, cheese) with 4 criteria — "not consume/rarely"; "1-2 times a month"; "1-2 times a week" and "daily/almost daily". Dairy products by fat content were grouped according to the criteria of Russian regulatory documents [23]. The criteria for assessing a diet were determined in accordance with the World Health Organization criteria [24].

Daily consumption of confectionery, sweets, and/or consumption >12 tsp/raw sugar lumps were considered "consuming too much added sugar". Excessive salt intake was determined when there were simultaneously 2 out of 3 following items in the diet: daily consumption of sausages and meat delicacies; daily consumption of pickles and marinades; adding more salt to cooked dishes. The protective dietary pattern included the 4 following items: daily consumption of vegetables and fruits, fish consumption at least 1-2 times a week, consuming only vegetable oils, and the consumption of low-fat dairy products.

Alcohol consumption was assessed by the frequency and intensity of its usual intake once and per week. The following types of alcoholic beverages were evaluated: beer, dry wines and champagne, fortified wines, house wines and liqueurs, spirits (vodka, cognac, etc.). Additionally, the calculation of ethanol consumption per day was carried out in total from each type of alcoholic beverages. The "high consumption" category included women consuming 84 g and men consuming 168 g of pure ethanol per week; "moderate consumption" — women consuming 42 g and men consuming 84 g of pure ethanol per week; "low consumption" — women consuming <42 g and men consuming <84 g ethanol per week.

AO was recorded at waist circumference (WC) ⩾102 cm in men and WC ⩾88 cm in women. Anthropometric measurements were carried out using standard techniques and is described in the study protocol [22].

Statistical analysis was carried out on a cohort of respondents who have complete data on dietary pattern (n=19297; men, 7342; women, 11955).

There were gaps in the answers about alcohol consumption. To recover the missing data in the answers to the questions "How often do you drink

Table 1

Prevalence of daily consumption of basic foods groups and eating disorders among respondents

	Without AO men n=5537, women n=6600		AO men n=1805, women n=5355		p
	n	%	n	%	
Red meat					
Men	2844	51,4	977	54,1	0,0412
Women	2434	36,9	2128	39,7	0,0014
Fish, seafood					
Men	587	10,6	228	12,6	0,0171
Women	567	8,6	629	11,7	<0,0001
Poultry					
Men	1454	26,3	438	24,3	0,0926
Women	1777	26,9	1644	30,7	<0,0001
Processed meat					
Men	1502	27,1	475	26,3	0,5001
Women	1263	19,1	1133	21,2	0,006
Pickles and marinades					
Men	626	11,3	190	10,5	0,3602
Women	564	8,5	552	10,3	0,001
Cereals, pasta					
Men	2397	43,3	704	39	0,0014
Women	2721	41,2	2095	39,1	0,0196
Fresh vegetables and fruits					
Men	2717	49,1	996	55,2	<0,0001
Women	4226	64	3635	67,9	<0,0001
Legumes					
Men	232	4,2	71	3,9	0,6343
Women	302	4,6	265	4,9	0,3401
Sweets, confectionery					
Men	2499	45,1	684	37,9	<0,0001
Women	3593	54,4	2567	47,9	<0,0001
Milk, kefir, yogurt					
Men	2482	44,8	795	44	0,562
Women	3493	52,9	2984	55,7	0,0023
Sour cream, cream					
Men	1197	21,6	353	19,6	0,0624
Women	1382	20,9	1092	20,4	0,4627
Cottage cheese					
Men	836	15,1	244	13,5	0,0997
Women	1371	20,8	1230	23	0,0038
Cheese					
Men	1963	35,5	650	36	0,6668
Women	2910	44,1	2340	43,7	0,6664
Adding more salt to cooked food					
Men	2634	47,6	892	49,4	0,1725
Women	2724	41,3	2251	42	0,4001
Excess salt intake					
Men	3497	63,2	1162	64,4	0,35
Women	3605	54,6	3048	56,9	0,0119

Table 1. Continuation

	Without AO men n=5537, women n=6600		AO men n=1805, women n=5355		p
	n	%	n	%	
Consuming too much added sugar (10% of the daily value or more)					
Men	2680	48,4	728	40,3	<0,0001
Women	3668	55,6	2608	48,7	<0,0001
Excessive intake of salt, sugar and milk fat					
Men	1673	30,2	475	26,3	0,0016
Women	1994	30,2	1477	27,6	0,0016
Cardioprotective diet					
Men	1311	23,7	525	29,1	<0,0001
Women	2255	34,2	2126	39,7	<0,0001

Abbreviation: AO — abdominal obesity.

Table 2

Daily food consumption, dietary habits and nutrition patterns of respondents with AO in comparison with those without AO*

	Men			Women		
	OR	95% CI	p	OR	95% CI	p
Daily consumption						
Red meat	1,12	1,00-1,25	0,0482	1,28	1,18-1,39	<0,0001
Fish, seafood	1,10	0,93-1,30	0,2750	1,26	1,11-1,44	0,0004
Poultry	0,93	0,82-1,06	0,2654	1,23	1,13-1,34	<0,0001
Processed meat	1,01	0,89-1,14	0,8890	1,14	1,03-1,26	0,0087
Pickles and marinades	0,92	0,77-1,10	0,3783	1,10	0,97-1,26	0,1504
Cereals, pasta	0,83	0,74-0,93	0,0010	0,89	0,82-0,96	0,0043
Fresh vegetables and fruits	1,13	1,01-1,27	0,0310	1,14	1,05-1,24	0,0017
Legumes	0,93	0,70-1,22	0,5929	0,96	0,80-1,15	0,6281
Sweets, confectionery	0,76	0,67-0,85	<0,0001	0,86	0,80-0,93	0,0002
Milk, kefir, yogurt	0,94	0,84-1,05	0,2715	1,11	1,03-1,20	0,0086
Sour cream, cream	0,86	0,75-0,99	0,0317	0,92	0,83-1,01	0,0786
Cottage cheese	0,81	0,68-0,94	0,0079	0,94	0,85-1,03	0,1668
Cheese	1,01	0,90-1,14	0,8154	0,96	0,89-1,04	0,3359
Eating disorders						
Excess salt intake	1,05	0,94-1,18	0,3967	1,04	0,96-1,13	0,3281
Adding more salt to cooked food	1,07	0,96-1,19	0,2416	0,99	0,92-1,08	0,8886
Excessive intake of salt and sugar	0,86	0,75-0,98	0,0236	0,88	0,81-0,97	0,0098
Excessive intake of salt, sugar and milk fat	0,84	0,74-0,95	0,0064	0,90	0,82-0,98	0,0145
Cardioprotective diet	1,17	1,03-1,33	0,0133	1,17	1,08-1,27	0,0002

Note: * — reference — persons without AO; standardization based on age, marital status, educational status, income level, type of residence, smoking status and level of alcohol consumption.
Abbreviations: AO — abdominal obesity, CI — confidence interval, OR — odds ratio.

alcohol?" and "How much do you usually drink in one meal?" data recovery algorithm was used. For each category of alcoholic beverages, a table was formed with the columns "sex", "age group", "education status", "type of residence", "average consumption frequency per week", "average quantity in ml per one meal". Every possible combination of values in the first four columns identified a subgroup to which the respondents might belong. For each subgroup, the mean values indicated in the last two columns were calculated. In the case when the respondent missed the answer to the question "How

Table 3

Comparison between groups of subjects with and without AO, depending on the level of alcohol consumption

	Men					Women				
	Without AO n=5537		AO n=1805		p	Without AO n=6600		AO n=5355		p
	n	%	n	%		n	%	n	%	
No consumption	909	16,4	317	17,6	0,2571	1380	20,9	1324	24,7	<0,0001
Low consumption	3406	61,5	963	53,4	<0,0001	4771	72,3	3688	68,9	<0,0001
Moderate consumption	901	16,3	352	19,5	0,0015	350	5,3	246	4,6	0,0764
High consumption	321	5,8	173	9,6	<0,0001	99	1,5	97	1,8	0,1824

Abbreviation: AO — abdominal obesity.

often do you drink alcohol?" or "How much do you usually drink in one meal?", the missing value was restored by the average of the column "Average consumption frequency per week" or "average quantity in ml per one meal", respectively, from the subgroup to which the respondent belonged.

Statistical analysis was performed using the Scipy 1.1.0, NumPy 1.14.3 libraries for Python 3.6.5 (Python Software Foundation, Delware, USA) and free R 3.6.1 environment. We calculated the mean and 95% lower and upper confidence intervals (CI) of the mean. The significance of differences between two independent samples was assessed using the Z-test for proportions in the case of binary data and the nonparametric Mann-Whitney U-test in the case of continuous one. The association between categorical data was assessed using the Pearson chi-squared test. The significance of differences between groups with different frequency of consuming a particular product was assessed using the Kruskal-Wallis test. For univariate and multivariate logistic regression, the glm function of the R 3.6.1 environment was used with an estimation of odds ratio (OR) and a 95% CI. The continuous variable "Age" was divided into 4 groups by decades ("25 years — 34 years" — the reference group, "35 years — 44 years", "45 years — 54 years", "55 years — 64 years") and was considered as a categorical. The results were considered significant at p<0,05.

Results

The central socio-demographic characteristics of subjects have already been presented in detail in previous publications [2].

The characteristics of the daily dietary patterns are presented in Table 1. There are significant differences in the dietary pattern of persons with AO, compared with those without AO. Thus, persons with AO, both men and women, more often consume red meat, fish and seafood, fruits and vegetables, less often sweets and confectionery, cereals and pasta. Also, persons with AO without sex differences are less likely to consume raw sugar. Sugar consumption per day among women with and without AO is 4,1 (4,0-4,2) vs 4,6 (4,5-4,7) tsp (p<0,0001), while among men: 5,4 (5,2-5,6) vs 6,2 (6,1-6,4), respectively (p<0,0001). Differences in consumption of other foods are observed only in women. So, Russian women with AO more often consume poultry, sausages and meat delicacies, pickles, liquid dairy products (milk, kefir, yogurt) and cottage cheese. Excessive salt intake among women with AO is observed significantly more often. It is noticeable that the diet of women with AO often contains foods with a high salt content (processed meat products, pickles), which form an excessive salt intake. There are no differences in the prevalence of adding more salt to cooked food among women with AO. Among men, these features are not observed. However, in the general population, the consumption of processed products among men is higher and is one of the population characteristics of dietary pattern [25].

Among people with AO, the consuming too much sugar is lower, and the pattern of excessive intake of salt, sugar and milk fat is less common. There is also a higher rate of people adhering to a healthy diet (adequate consumption of vegetables and fruits, fish products, using only vegetable oils and consumption of low-fat dairy products).

The logistic regression made it possible to detail the differences in the diet of individuals with AO, as well as to demonstrate sex differences. The results of the analysis are presented in Table 2. Thus, among the differences in the dietary pattern of men with AO compared with those without AO, only a higher consumption of red meat and fruit and vegetable products remained, while rarer — cereals, pasta, sweets, including confectionery, cottage cheese and high-fat dairy products (sour cream and cream). In the diet of women with AO, a wider range

Table 4

Characteristics of the frequency and intensity of alcohol consumption depending on the AO

	Men					Women				
	No AO, n=5537		AO, n=1805		p	No AO, n=6600		AO, n=5355		p
	M	CI (lower-upper)	M	CI (lower-upper)		M	CI (lower-upper)	M	CI (lower-upper)	
Beer										
% of those who consume	54,11		48,48		<0,0001	32,91		25,14		<0,0001
Consumption frequency, times a week	1,02	0,98-1,07	1,04	0,95-1,12	0,9907	0,50	0,47-0,53	0,46	0,43-0,49	0,0002
Intensity per meal, ml	946,50	922,93-970,07	1068,77	1018,63-1118,91	<0,0001	568,75	551,99-585,50	534,82	511,29-558,36	<0,0001
Intensity per week, ml	985,09	931,77-1038,42	1153,30	1034,71-1271,89	0,0038	319,76	294,34-345,18	287,65	256,70-318,60	<0,0001
Dry wines, champagne										
% of those who consume	33,56		28,86		0,0002	60,08		50,10		<0,0001
Consumption frequency, times a week	0,35	0,32-0,38	0,40	0,34-0,46	0,0174	0,28	0,26-0,29	0,26	0,24-0,27	<0,0001
Intensity per meal, ml	300,15	289,46-310,85	326,18	302,35-350,02	0,3205	244,22	238,95-249,48	226,05	220,40-231,70	<0,0001
Intensity per week, ml	107,42	97,33-117,51	138,59	112,29-164,89	0,0290	71,51	66,74-76,28	61,32	56,55-66,08	<0,0001
Fortified wines										
% of those who consume	7,30		7,53		0,7758	7,06		6,80		0,5983
Consumption frequency, times a week	0,31	0,24-0,38	0,43	0,26-0,60	0,0391	0,22	0,17-0,26	0,24	0,18-0,30	0,2120
Intensity per meal, ml	263,77	240,89-286,64	314,57	263,18-365,97	0,2623	198,16	185,61-210,70	185,45	172,20-198,70	0,1508
Intensity per week, ml	95,92	63,87-127,97	149,94	83,85-216,03	0,0220	43,59	35,00-52,18	46,19	35,99-56,38	0,5323
Homemade liqueurs										
% of those who consume	7,46		7,81		0,6569	5,23		4,84		0,3534
Consumption frequency, times a week	0,50	0,41-0,58	0,50	0,36-0,64	0,3091	0,30	0,22-0,37	0,29	0,21-0,36	0,8383
Intensity per meal, ml	254,25	228,65-279,85	248,14	213,67-282,61	0,8687	159,01	142,59-175,44	146,64	133,97-159,31	0,5706
Intensity per week, ml	119,07	92,01-146,13	112,47	88,92-136,02	0,1915	63,75	21,84-105,67	39,09	30,08-48,11	0,6251
Vodka, cognac and other spirits										
% of those who consume	68,16		72,08		0,0019	35,00		41,76		<0,0001
Consumption frequency, times a week	0,57	0,55-0,60	0,69	0,64-0,74	<0,0001	0,29	0,27-0,32	0,31	0,29-0,33	0,0002
Intensity per meal, ml	240,38	233,98-246,77	271,6	259,88-283,31	<0,0001	129,2	125,55-132,85	131,47	127,11-135,83	0,5645
Intensity per week, ml	133,09	126,38-139,79	176,2	164,14-188,26	<0,0001	39,37	35,39-43,35	42,50	39,03-45,98	0,1295

Abbreviations: AO — abdominal obesity, CI — confidence interval.

Table 5

Distribution of mean WC values by frequency of consuming main food groups*

	Do not consume/rarely		1-2 times a month		1-2 times a week		Daily/almost daily		p**
	M	SD	M	SD	M	SD	M	SD	
Men, n=7860									
Red meat	94,0	13,4	92,1	14,1	92,3	13,8	93,5	13,3	<0,0001
Fish, seafood	89,9	13,5	92,0	13,8	93,4	13,5	94,4	13,1	<0,0001
Poultry	92,6	13,0	92,1	13,3	93,4	13,6	92,3	13,6	0,00656
Processed meat	93,5	13,1	92,8	13,8	93,0	13,6	92,6	13,8	0,28688
Pickles and marinades	92,6	13,6	92,5	13,2	93,9	13,7	91,9	13,9	<0,0001
Cereals, pasta	94,6	14,8	93,1	13,9	93,7	13,4	91,9	13,4	<0,0001
Fresh vegetables and fruits	93,9	14,4	91,4	13,6	92,3	13,7	93,7	13,4	<0,0001
Legumes	92,6	13,7	93,3	13,4	92,9	13,6	92,3	13,7	0,15308
Sweets, confectionery	95,1	14,4	93,2	14,0	92,9	13,9	92,2	12,8	<0,0001
Milk, kefir, yogurt	93,8	13,4	92,3	13,3	92,8	14,1	93,1	13,2	0,09485
Sour cream, cream	93,8	13,8	92,5	13,4	93,2	13,9	92,2	12,8	0,02455
Cottage cheese	93,5	13,9	92,7	13,3	93,1	13,6	92,2	13,3	0,11555
Cheese	93,6	13,7	93,0	13,7	92,9	13,5	92,8	13,5	0,70581
Women, n=13100									
Red meat	87,3	16,1	86,1	15,2	86,1	14,9	86,9	15,1	0,01723
Fish, seafood	85,3	15,4	84,7	14,8	87,1	15,1	89,0	15,5	<0,0001
Poultry	86,5	16,6	85,6	15,2	86,2	14,8	87,3	15,6	0,00024
Processed meat	86,5	14,7	85,6	15,1	86,6	15,4	87,1	15,3	0,00083
Pickles and marinades	86,7	14,9	85,4	15,1	86,9	15,2	88,2	15,6	<0,0001
Cereals, pasta	88,9	15,2	87,2	15,3	86,4	15,1	85,9	15,1	<0,0001
Fresh vegetables and fruits	90,1	15,7	85,0	15,2	85,2	15,0	86,9	15,1	<0,0001
Legumes	86,9	15,0	85,9	15,1	86,6	15,4	86,5	15,4	0,00095
Sweets, confectionery	90,7	15,9	87,7	15,7	86,6	15,3	85,1	14,5	<0,0001
Milk, kefir, yogurt	87,5	14,9	85,1	14,9	85,9	15,2	86,8	15,1	<0,0001
Sour cream, cream	88,2	15,4	85,5	15,4	86,3	14,6	86,2	15,5	<0,0001
Cottage cheese	86,3	15,6	85,4	15,4	86,8	14,9	86,9	14,8	<0,0001
Cheese	88,6	16,2	86,9	16,1	86,1	15,1	86,3	14,6	0,00042

Note: * — expanded sample of subjects excluding alcohol consumption and smoking status, ** — p — value is given for the difference between groups of different product consumption frequency according to the Kruskal-Wallis test.
Abbreviations: M — sample mean, SD — standard deviation.

of differences is noted. There was more common consumption of not only red meat, but fish products, poultry, meat and sausage products, and liquid dairy products, as well as fruits and vegetables, while there is a rarer presence in the diet of cereals, pasta, sweets, and high-fat dairy products (sour cream, cream). However, in this analysis, there are no longer any differences in excessive salt intake among women with AO. Of the positive aspects of the diet, both among men and women with AO, there is a rarer excessive consumption of sugar, salt, milk fat, and a more common use of cardioprotective diet.

Significant differences are observed in the level of alcohol consumption. So, among men with AO, the indicator is lower in the category "low consumption" and higher in the categories "moderate consumption" and "high consumption" (Table 3). Among men with AO, the percentage of people with a high alcohol consumption significantly higher than in those without AO (OR, 1,72 (95% CI 1,42-2,09), p<0,0001). In women, the situation is the opposite: persons with AO are less likely to consume alcoholic beverages. Thus, the indices in "non-users" group are higher, and in the group of "low consumption" — lower in comparison with similar indices in women without AO (p<0,0001). There are no significant differences in the categories "moderate consumption" and "high consumption". The characteristics of alcohol consumption by persons with and without AO are presented in Table 4.

Men with AO, compared with men without AO, have a higher frequency and intensity of consuming dry and fortified wines, strong drinks (vodka, cognac). Differences were also observed in the form of greater intensity of beer consumption by men with AO. Among women, the situation is the opposite: persons with AO are less likely to consume alcoholic beverages. There was a lower frequency and intensity of beer and dry wine consumption among women with AO compared to those without AO. However, the frequency of drinking spirits among women with AO is higher, but without significant differences in intensity. In general, men with AO showed a positive association with alcohol consumption (χ=53,64, p<0,0001), while women with AO had a negative association (χ=28,63, p<0,0001).

The average WC values depending on the consumption of a particular food product are presented in Table 5. There are significant differences in WC among men between groups with different frequency of consumption of most food products analyzed in the study (red meat, fish, poultry, pickles, vegetables/fruits, cereals, sweets), with the exception of meat and sausage products, legumes, and dairy products, except for sour cream/cream. Among women, significant differences in WC are observed with different frequency of consumption of all analyzed food products.

Discussion

The performed analysis demonstrates differences in dietary pattern of persons with AO in comparison with Russians without AO. These differences are observed both in men and women with AO. In women, there are more differences than in the diets of men, which is reflected in the more frequent consumption of animal and processed products. Sex differences can also be traced in the level of alcohol consumption. Thus, men with AO more often and with higher intensity consume alcoholic beverages, in contrast to women with AO, in whom these indicators are lower than in those without AO.

It is also noticeable that persons with AO are more likely to consume energy-intensive foods — red meat, as well as men with AO — also alcoholic beverages, and women with AO — processed meat and sausages, liquid dairy products, fish and poultry.

The habit of consuming dairy products, even at the population level, is very widespread [25, 26]. Therefore, the analysis of association between consuming dairy products and the obesity is of interest in many studies [10-18]. However, the results of analyzes are very different: from AO risk reduction [10, 12, 14-16] and the absence of differences [9, 10] to positive associations with certain types of dairy products [17]. Results similar to those obtained in this study regarding higher consumption of milk, kefir and yogurt in women with AO were also noted in another Russian study [11], carried out using the "Selective observation of the diet of the population" conducted in 2013 [27]. However, after standardization for age, educational status and income level, association was observed only in men, in contrast to the present study. The consumption of cottage cheese in women was associated with a decrease in obesity risk [11]; in the present study, no significant associations were found. It should be noted that the cited and present studies differed in anthropometric measurements and, accordingly, determining the body weight category. In the present study, anthropometric measurements were carried out according to standard methods by physician investigators, and in "Selective observation of the diet of the population" — by the respondents themselves. However, despite some differences in the results obtained, in general, there were positive associations between the consumption of liquid dairy products (in particular, kefir) and the obesity.

In the present study, no associations of consuming too much added sugar, confectionery and other sweets with the AO were observed, which may be related to the assessment of consumption frequency, but not intensity, as in other studies [19]. However, results similar to the present ones were obtained in another study [6], which included 2043 persons of both sexes from Moscow, Kaluga, Michurinsk and Tambov. The study demonstrated that, despite the overall high intake of added sugar from various foods, there was no association with obesity among the respondents [6].

The positive association of high consumption of red meat and the obesity [9] is confirmed in almost all studies on this topic. The present analysis also noted a higher consumption of red meat in both men and women with AO.

The positive association noted by many researchers of the common consumption of processed red meat (sausages and meat delicacies) and the presence of general and AO [6, 19] is also observed in this analysis among women. Alcohol use has also been positively associated with obesity in studies [14], whereas in the current analysis this has been confirmed among men.

In general, the analysis demonstrates both unfavorable accents in the nutritional pattern of persons with AO, and at the same time, protective ones in comparison with persons without AO. Among persons with AO of both sexes, along with a higher consumption of red meat, a higher presence of vegetables and fruits in the diet is also noted. Also, among persons with AO without sex differences, the cardioprotective nutrition pattern is more common. Among the unfavorable dietary characteristics of persons with AO, the consumption of energy-intensive foods without significant nutritional value — alcoholic beverages for both sexes, as well as processed meat — for women. One should also take into account the general dietary disturbances: low daily consumption of fruits and vegetables, cereals, legumes; high consumption of red meat, processed meat, and confectionery [25, 26].

This analysis clearly demonstrated the dietary characteristics of individuals with AO and revealed sex differences. The nutritional imbalance observed in individual diets is not always reflected in the population analysis. However, this analysis demonstrates a lot of emphasis on disorders in the eating habits of people with AO, which forms a scientifically grounded basis for preventive and rehabilitative measures. The research results can be used in developing preventive population-based programs aimed at preventing obesity, in estimating public health indicators and in making targeted management decisions.

Relationship and Activities: none.

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Russian Journal of Cardiology 2021;26(5):4399
doi:10.15829/1560-4071-2021-4399
https://russjcardiol.elpub.ru

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Association of high-sensitivity C-reactive protein with fatal and non-fatal cardiovascular events in working-age people: data from the ESSE-RF study

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Aim. To study the relationship of different levels of high-sensitivity C-reactive protein (hs-CRP) with cardiovascular events and assess its contribution to the development of outcomes in Russian regions.

Material and methods. The work used the data from the multicenter study ESSE-RF — a representative sample of male and female population aged 25-64 years. All participants signed informed consent. The study included 10421 people (women, 6399 (61,4%)). The cohort was followed up from 2012 to 2019 (median follow-up period, 5,5 years). A hard endpoint (cardiovascular mortality and nonfatal myocardial infarction (MI)) was determined in 187 people, while a soft endpoint (nonfatal MI, stroke, revascularization, heart failure progression and cardiovascular mortality) — in 319 people.

Results. The results showed that hs-CRP is significantly associated with the main risk factors (with the exception of low-density lipoproteins). At the same time, it was found that optimal hs-CRP level for predicting the risk of cardiovascular events (CVE) in Russian population is significantly lower than 3 mg/L, but higher than 1 mg/L (1,54/1,89 mg/dL for men and women, respectively). Adding hs-CRP to sex and age significantly improved risk prediction (AUC, 79,7; 95% CI, 77,8-81,7). At the same time, adding a wide list of confounders to hs-CRP, sex and age does not improve the model's predictive value (AUC, 79,7; 78,2-82,1).

Conclusion. This study for the first time showed a significant independent contribution of hs-CRP to CVEs development in the Russian population, and the addition of hs-CRP to sex and age significantly increased the predictive value of model.

Keywords: high-sensitivity C-reactive protein, cardiovascular events, risk factors.

Relationships and Activities. The ESSE-RF prospective study was carried out within the state assignment № AAAA-A17-117070760036-6.

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Received: 07.03.2021
Revision Received: 16.03.2021
Accepted: 03.05.2021

For citation: Evstifeeva S. E., Shalnova S. A., Kutsenko V. A., Yarovaya E. B., Balanova Yu. A., Imaeva A. E., Kapustina A. V., Muromtseva G. A., Maksimov S. A., Karamnova N. S., Samokhina Yu. Yu., Drapkina O. M., Kulakova N. V., Trubacheva I. A., Efanov A. Yu., Shabunova A. A., Belova O. A., Rotar O. P. on behalf of the ESSE-RF researchers. Association of high-sensitivity C-reactive protein with fatal and non-fatal cardiovascular events in working-age people: data from the ESSE-RF study. *Russian Journal of Cardiology*. 2021;26(5):4399. (In Russ.) doi:10.15829/1560-4071-2021-4399

Based on numerous studies, now there is a concept of additional or novel risk factors (RFs), which, together with the classical factors, increase the predictive power. In recent years, the researchers actively searched for novel biomarkers.

One of these biomarkers is C-reactive protein (CRP), which is a marker of inflammation. This unusual, "bifacial" biomarker brings us more and more surprises. Dozens of years have passed since the CRP discovery by Tilet W and Francis T (1930) [1], but a new CRP role was identified after the discovery of a high-sensitivity technique for measuring CRP (1994-1997), which allowed researchers to look at the problems of nonspecific inflammation from a different angle.

Subsequently, it became known that high-sensitivity CRP (hs-CRP) level increases sharply during the inflammatory response, causing coronary artery damage due to the direct activation of endothelial cells. Factors causing artery spasm contribute to the formation of microthrombi and impaired microcirculation, which has a strong effect on plaque development. In an experimental study, it was shown that this process requires a transition from pentameric CRP to its monomeric conformation (mCRP) [2].

Given the discovery of vesicular transport system, we now know that exosomes can carry different cell components, including proteins and lipids [3]. The study by Melnikov I.S. et al. (2019) suggested that in patients with coronary artery disease (CAD), blood increase in circulating exosomes carrying mCRP and leukocyte markers on their surface, as well as the mCRP in atherosclerotic areas, may indicate the participation of mCRP in the pathogenesis of coronary atherosclerosis [4].

In 2001, the American Heart Association published guidelines for determining hs-CRP to stratify the risk of cardiovascular diseases (CVD), in particular CAD, in the moderate risk group [5].

Finally, the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER study) showed that statins, regardless of total cholesterol (TC) levels, reduced hs-CRP concentration, which decreased the risk of cardiovascular events (CVE) [6].

However, despite the evidence from numerous studies, the data are contradictory, especially when it comes to the relationship between hs-CRP and the death risk among population.

The aim was to study the relationship of different levels of high-sensitivity C-reactive protein (hs-CRP) with cardiovascular events and assess its contribution to the development of outcomes in Russian regions.

Material and methods

The object of the ESSE-RF multicenter study was representative samples of male and female population aged 25-64 years from 6 Russian regions (Vladivostok, Vologda, Ivanovo, St. Petersburg, Tomsk, Tyumen). A multistage stratified sample was selected using the Kish grid [7]. The study was approved by the local ethics committee. All subjects signed informed consent. In general, the response rate was 80,0%. A detailed protocol for the ESSE-RF study was published earlier [8].

A total of 10421 people were studied, including 4022 (38,6%) men and 6399 (61,4%) women. Sociodemographic parameters included sex, age, region, income.

The presence of a prior disease was considered with a positive answer to the question: "Have a doctor ever told you that you have/had the following diseases?: hypertension (HTN), CAD (angina), myocardial infarction (MI), stroke (cerebral vessel thrombosis or hemorrhage), rheumatoid arthritis (RA), cancer, chronic bronchitis, Parkinson's disease (PD)". Smoking status was assessed: never smoked, former smoking, current smoking.

Instrumental diagnostic tests. Blood pressure (BP) was measured twice on the right arm in a sitting posture with a brief in between break (2 min) using an automatic BP monitor OMRON M3 Expert (Japan).

All anthropometric measurements were performed routinely, as in most studies. In the study, the body mass index (BMI) was calculated using the Quetelet's equation (BMI = Height (m) / Weight (kg^2)). Abdominal obesity (AO) was considered as a waist circumference ⩾102/88 cm for men and women.

Laboratory diagnostic tests. In all centers, blood was drawn from the cubital vein after 12 hours of fasting. Blood serum was obtained by low-speed centrifugation at 900g for 20 min at a temperature of +4° C. Biological material samples were frozen and stored at a temperature not exceeding -20° C until they were sent to the federal center. The transportation of biomaterials was carried out by specialized services. The lipid profile parameters, including the levels of triglycerides (TG), glucose and hs-CRP, were determined using an Abbott Architect c8000 analyzer using diagnostic kits from Abbott Diagnostic (USA). Standardization and quality control of the analysis was carried out in accordance with the requirements of the Federal system for external quality control of clinical laboratory procedures.

Hs-CRP was studied in grades of low, moderate and high cardiovascular risk. The hs-CRP values of 3-10 mg/L were taken as the increased level [9].

Prospective follow-up of the cohort from 2012 to 2019 (median follow-up, 5,5 years) revealed hard endpoint (CVD mortality and nonfatal MI) in 187

Table 1

Multivariate regression analysis of the association of hs-CRP with risk factors, adjusted for regions

Parameter	Level of hs-CRP increase depending on the increase in the parameter*	CI	p
+10 years	1,06	(1,04-1,09)	0,0001
Male	0,81	(0,77-0,85)	0,0001
Current smoker	1,12	(1,06-1,17)	0,0001
+10 mm Hg SBP	1,02	(1,01-1,03)	0,001
AHT	1,08	(1,02-1,14)	0,006
+1 logTG	1,32	(1,26-1,39)	0,0001
+1 mmol/L HDL-C	0,81	(0,75-0,87)	0,0001
+1 mmol/L LDL_C	1,02	(1,00-1,04)	0,124
+1 logGlu	1,40	(1,24-1,58)	0,0001
+1 BMI kg/m^2	1,07	(1,06-1,07)	0,0001
+1 logLp(a)	1,02	(1,00-1,04)	0,046
Prior diseases			
Parkinson's disease	1,11	(0,60-2,04)	0,740
Rheumatoid arthritis	1,11	(1,02-1,21)	0,017
Chronical bronchitis	1,07	(1,00-1,14)	0,055
MI	1,05	(0,89-1,24)	0,577
Stroke	1,01	(0,87-1,19)	0,872
CAD	0,96	(0,88-1,04)	0,330
Arrhythmias	1,03	(0,97-1,09)	0,389
Cancer	1,06	(0,93-1,20)	0,383

Note: * — how many times higher is the level of hs-CRP in the risk group or when the continuous parameter is increased by the specified value.

Abbreviations: AHT — antihypertensive therapy, hs-CRP — high-sensitivity C-reactive protein, CI — confidence interval, CAD — coronary artery disease, BMI — body mass index, MI — myocardial infarction, LP(a) — lipoprotein (a), SBP — systolic blood pressure, TG — triglycerides, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, log — logarithm.

(1,79%) people and soft endpoint (nonfatal MI and stroke, revascularization, heart failure (HF) progression and CVD mortality) in 319 (3,06%) people. The HF progression was considered as the hospitalization due to the disease severity (increase in stage and/or decrease in functional class).

The analysis of the following models (M) was carried out: M1 — hs-CRP; M2 — M1+sex, age; M3 — M2+TC, HTN, PD, RA, bronchitis; M4 — M3+TG, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), glucose, AO.

The central results of descriptive analysis were presented earlier [10].

Statistical data analysis. Statistical analysis was carried out using the R 3.6.1 environment. To assess the associations of hs-CRP and RFs, a linear regression model was used, where the logarithm of hs-CRP was used as a dependent variable. The Kaplan-Meier survival curves were used to estimate the probability of survival at a certain point in time. Comparison of two survival curves was carried out using the log-rank test. When comparing three or more survival curves, the Holm correction for multiple comparisons was applied. The Cox proportional hazards model

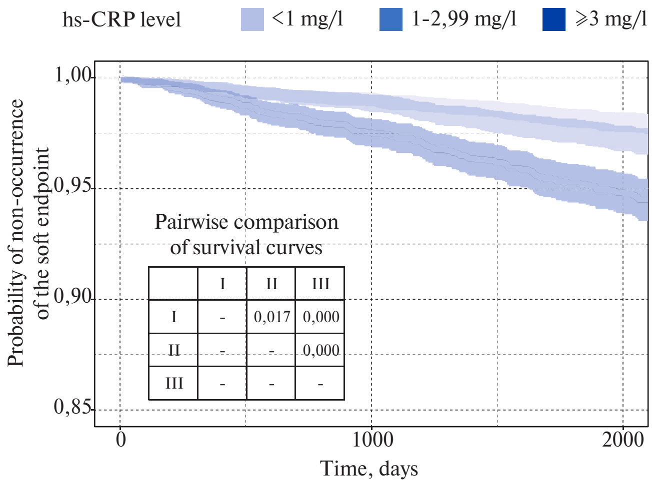


Figure 1. Kaplan-Meier curves of study participants depending on hs-CRP level for the soft endpoint.
Abbreviation: hs-CRP — highly sensitive C-reactive protein.

Table 2

Associations of hard endpoint with hs-CRP in models

Variables in the model	Q4 sex-specific Hs-CRP (1,54/1,89)	Q5 sex-specific Hs-CRP (3,16/3,88)	Hs-CRP >1 mg/L	Hs-CRP >3 mg/L
	RR [95% CI]			
M1	2,59 [1,93-3,48]*	2,4 [1,79-3,22]*	2,01 [1,45-2,77]*	2,32 [1,74-3,11]*
M2	2,00 [1,48-2,02]*	1,77 [1,31-2,38]*	1,52 [1,09-2,11]*	2,76 [1,39-2,5]*
M3	1,91 [1,42-2,59]*	1,67 [1,24-2,26]*	1,4 [1,01-1,95]*	1,8 [1,34-2,42]*
M4	1,78 [1,31-2,43]*	1,55 [1,13-2,12]*	1,28 [0,91-1,8]	1,67 [1,22-2,27]*

Note: * — p<0,05; ** — -region-adjusted models (M). M1 — hs-CRP; M2 — M1+sex, age; M3 — M2+TC, HTN, PD, RA, bronchitis; M4 — M3+TG, HDL-C, LDL-C, glucose, AO; Q — sex-specific quintiles, LDL-C — low density lipoprotein cholesterol ⩾3 mmol/l, HDL-C — high-density lipoprotein cholesterol ⩽1,0/1,2 mmol/L for men and women, respectively, TG — triglycerides ⩾1,7 mmol/L, AO — abdominal obesity (waist circumference — WC ⩾102/88 cm for men and women, respectively), glucose ⩾5,6 mmol/L.

Abbreviations: HTN — hypertension, AO — abdominal obesity, hs-CRP — highly sensitive C-reactive protein, CI — confidence interval, M — model, WC — waist circumference, TC — total cholesterol, RA — rheumatoid arthritis, TG — triglycerides, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, Q — quintiles, RR — relative risk.

Table 3

Associations of the soft endpoint with hs-CRP in models

Variables in the model	Q4 sex-specific Hs-CRP (1,54/1,89)	Q5 sex-specific Hs-CRP (3,16/3,88)	Hs-CRP >1 mg/L	Hs-CRP >3 mg/L
	RR [95% CI]			
M1	2,4 [1,91-3,01]*	2,29 [1,83-2,86]*	1,92 [1,51-2,46]*	2,23 [1,79-2,79]*
M2	1,9 [1,51-2,39]*	1,73 [1,38-2,17]*	1,45 [1,13-1,86]*	1,23 [1,46-2,3]*
M3	1,8 [1,43-2,27]*	1,62 [1,29-2,04]*	1,36 [1,06-1,75]*	1,75 [1,39-2,2]*
M4	1,72 [1,35-2,19]*	1,57 [1,24-2]*	1,3 [1-1,68]*	1,67 [1,32-2,12]*

Примечание: ; Q — sex-specific quintiles, LDL-C — low density lipoprotein cholesterol ⩾3 mmol/l, HDL-C — high-density lipoprotein cholesterol ⩽1,0/1,2 mmol/L for men and women, respectively, TG — triglycerides ⩾1,7 mmol/L, AO — abdominal obesity (waist circumference — WC ⩾102/88 cm for men and women, respectively), glucose ⩾5,6 mmol/L; * — p<0,05; ** — -region-adjusted models (M). M1 — hs-CRP; M2 — M1+sex, age; M3 — M2+TC, HTN, PD, RA, bronchitis; M4 — M3+TG, HDL-C, LDL-C, glucose, AO.

Abbreviations: HTN — hypertension, AO — abdominal obesity, hs-CRP — highly sensitive C-reactive protein, CI — confidence interval, M — model, WC — waist circumference, TC — total cholesterol, RA — rheumatoid arthritis, TG — triglycerides, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, Q — quintiles, RR — relative risk.

(Cox regression) was used to predict the risk of cardiovascular death or adverse event (CAD, including MI, stroke, revascularization, HF) and to assess the effect of predetermined independent variables on this risk. Additionally, age was included as an independent variable in each of the Cox regressions presented. If the results were presented without separating by sex, then the variable “sex” was also added to the independent variables. The relative risk (RR) and 95% confidence interval [95% CI] were calculated. The Receiver Operator Characteristic (ROC) analysis was carried out. For all types of analysis described, the differences were considered significant at p<0,05.

Results

Multivariate regression analysis, adjusted for regions, revealed that hs-CRP level in men is 20% lower than in women, and in current smokers, regardless of sex — 10% higher. The hs-CRP level is significantly positively associated with an increase in age, systolic ИЗ, BMI, TG, glucose (p<0,0001), antihypertensive therapy (p<0,006) and is inversely associated with HDL-C (p<0,0001). No association with LDL-C was found. In the multivariate model, significant associations with prior diseases persisted only for RA (p=0,017) (Table 1).

It should be noted separately that the association of CRP level with age is different for men and women. Dependence of the average CRP logarithm on sex and age: loghs-CRP = -1,09+0,267 (men) + 0,023 (age in years, if a man) + (age in years, if a woman). That is, at 25 years of age, hs-CRP is 10% higher in men than in women. Every ten years, the level of hs-CRP rises by 12% in men and 15% in women. At 39 years old, hs-CRP levels became equal, and by age 65, hs-CRP levels in women are 50% higher than in men.

Survival curves for soft endpoints with Holm correction demonstrate a significant relationship with the hs-CRP level. The analysis was carried out in three groups of CRP: low risk — up to 1 mg/L, moderate — 1-2,99 mg/L, and high risk — ⩾3 mg/L. Pairwise analysis showed that all curves are pairwise different, and the higher the hs-CRP level, the lower the survival rate (Figure 1).

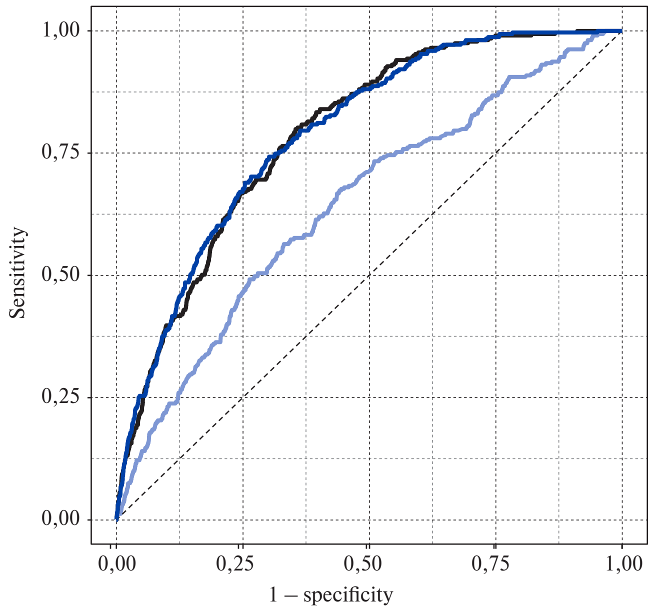
In order to clarify the hs-CRP risk levels in population, a ROC analysis was performed, which showed that the optimal cut-off point for predicting a soft endpoint is 1,49 mg/L for men and 1,83 mg/L for women, which is close to the fourth quintile (Q4: men — 1,54 mg/L; women — 1,89 mg/L). Therefore, in further analysis, we used the Q4 as a cut-off point.

Cox regression showed significant associations of hs-CRP with hard endpoints regardless of the model (M), with the exception of M4 with hs-CRP >1 mg/L, where no significant association was found (RR, 1,28 [0,91-1,8], p>0,05). The highest risk was already noted in M1 at Q4, which is very slightly inferior to currently accepted point of the increased hs-CRP level (>3 mg/L). Comparison of M1 and M2 did not show the significant RR change, which speaks in favor of a pronounced association of isolated hs-CRP with hard endpoint (Table 2).

A similar data was obtained when analyzing various levels of hs-CRP with soft endpoint, where significant associations were found in all models (Table 3).

The analysis of proportional hazard models showed a rather pronounced and independent role of CRP in the development of both hard and soft endpoints.

ROC analysis for soft endpoints revealed that isolated hs-CRP has an area under the ROC curve equal to 64,2%, which significantly increases to 79,7 when sex and age are added to the model. Further addition of a wide list of confounders did not significantly increase the area under the ROC curve. In other words, it does not significantly increase the predictive power of the model (Figure 2).



Model parameters*	AUC (95% CI)
hs-CRP	64,3 (61,5-67,1)
hs-CRP, gender, age	79,7 (77,8-81,7)
hs-CRP, gender, age, smoking, HTN, LDL-C, HDL-C, TG, glucose	80,2 (78,2-82,1)

Figure 2. ROC analysis of predictive power of continuous risk factors.

Note: * — adjusted for study regions.

Abbreviations: HTN — hypertension, hs-CRP — highly sensitive C-reactive protein, CI — confidence interval, TG — triglycerides, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, AUC — area under the ROC curve.

Discussion

The results obtained in our study including more than 10 thousand people showed that an increased level of hs-CRP is a reliable and independent predictor of CVE in the Russian population, even with significant relationships with the main RFs and RA, which is one of the most prominent representatives of chronic inflammatory diseases, and its relationship with hs-CRP is not in doubt among most researchers [10]. At the same time, it was found that the hs-CRP level, which is optimal for predicting the CVE risk, in Russian population is significantly lower than 3 mg/L, but higher than 1 mg/L (Q4 — 1,54/1,89 mg/L in men and women, respectively). This shows that above these levels, hs-CRP has a significantly higher risk of CVE than at lower levels, and slightly higher than at an hs-CRP ⩾3 mg/L. Notably, adding hs-CRP to sex and age significantly improves risk prediction. In other words, the negative effect of increased hs-CRP begins at its lower values It is important to emphasize that adding a broad list of confounders to hs-CRP, sex and age does not improve the predictive power of the model. Over the past decade, more than 20 prospective cohort studies have shown that hs-CRP levels are independently associated with future risk of MI, stroke, metabolic syndrome, and type 2 diabetes. Most studies with adequate sample sizes have demonstrated that hs-CRP adds predictive information to the risk stratification.

Some studies have reported conflicting data on the association between hs-CRP and mortality risk in the population. Thus, the meta-analysis of 14 studies (up to October 2016, n=83995), studying the effect of elevated baseline hs-CRP levels on cancer, CVD, or all-cause mortality in the general population, showed that when comparing the highest versus lowest hs-CRP level, RR was 1,25 [95% CI, 1,13-1,38] for cancer mortality, 2,03 [95% CI, 1,65-

2,50] for CVD mortality, and 1,75 [1,55-1,98] for all-cause mortality [11]. Subgroup analyzes showed an effect of elevated hs-CRP levels on cancer mortality in men but not in women [RR, 1,03; 0,83-1,27]. The authors conclude that elevated hs-CRP levels can independently predict the risk of mortality from CVD in a population [11]. The National Health and Nutrition Examination Survey (NHANES III) also found an association of high hs-CRP with all-cause mortality (RR, 1,80 [1,32-2,46], p=0,001) and CVD (RR, 1,54 [1,08-2,18]) in men. However, modelling did not confirm the association of a high hsCRP levels with CVD mortality [12].

In turn, according to recently published meta-analysis of 22 studies, comparison of moderate hs-CRP to low hs-CRP levels showed the RR of 1,30 [1,20-1,41] and 1,43 [1,22-1,68] for all-cause and CVD mortality, respectively. In the group with high hs-CRP, the RR was 1,75 [1,59-1,92], 2,02 [1,70-2,41], 1,32 [1,21-1,45] for all-cause, CVD, and cancer mortality. This meta-analysis demonstrated that the relationship between hs-CRP and mortality was non-linear for all-cause and CVD mortality and linear for cancer and non-cardiovascular mortality [13].

Recently published results of the Brazilian study showed a significant association of hs-CRP with all-cause mortality in a multivariate model [14].

The studies with an Asian population demonstrated that hs-CRP level in Asians is reduced in comparison with white Europeans [15, 16]. Thus, the median hs-CRP level in the Korean population is 0,6 (95% CI, 0,3-1,3) in men and 0,4 (0,1-1,1) in women ($p<0,001$). Only 8,6% of men and 6,2% of women reached the standard cut-off point for hs-CRP >3 mg/L, which is the upper tertile in the Caucasian population. Moderate-risk hs-CRP models improved the reclassification of CVD mortality risk by 24,9% (p=0,04). Standard cutoff points for CRP in the Asian population may lead to risk underestimation [17]. In addition, both Asian and European studies indicate the need for additional analysis to study the sex contribution at different age periods to unfavorable risk.

Conclusion

This study for the first time showed a significant independent contribution of hs-CRP to CVEs development in the Russian population, and the addition of hs-CRP to sex and age significantly increased the predictive value of model.

Relationships and Activities. The ESSE-RF prospective study was carried out within the state assignment № AAAA-A17-117070760036-6.

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Changes in mortality rates from acute types of coronary artery disease in Russia for the period from 2015 to 2019

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Aim. To identify regional specifics of changes in mortality rates from acute types of coronary artery disease (CAD) in 82 Russian regions for the period from 2015 to 2019.

Material and methods. The study used data from the Federal State Statistics Service of Russia on mortality from acute CAD types in 82 Russian regions. Standardized death rates (SDRs) for 2015 and 2019 were estimated based on the European standard. We analyzed the SDRs of the population from acute (primary) and recurrent myocardial infarction (MI), other acute CAD types (I21-I22, I24.8 in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)).

Results. Over the period from 2015 to 2019, mortality from all acute CAD types decreased by 21%, from acute MI — by 9%, from recurrent MI — by 22%, from any MI (acute/recurrent) recurrent — by 14%, and from other CAD types — by 21%. A decrease in mortality from all acute CAD types was recorded in 69 regions, from acute MI — in 58 regions, and recurrent MI — in 62 regions. However, a simultaneous decrease in SDRs from each of the acute CAD types (acute MI, recurrent MI and other acute CAD types) for the period 2015-2019 occurred only in 29 Russian regions. An increase in mortality from all acute CAD types was noted in 14 regions and from any MI — in 21 regions. The coefficient of variation (Cv) for recurrent MI and other acute CAD types of 69% and 103%, respectively, in 2015 and its growth (up to 75% and 134%, respectively) by 2019 indicate growing problems with the coding of death causes.

Conclusion. In 2019, compared to 2015, a decrease in mortality from acute CAD types was recorded in most Russian regions. The identified regional specifics require clarification of approaches to death cause coding and the introduction of additions to mortality reduction programs, taking into account the specifics of each Russian region.

Keywords: coronary artery disease, myocardial infarction, mortality, ICD-10.

Relationships and Activities: none.

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Received: 01.04.2021
Revision Received: 01.05.2021
Accepted: 03.05.2021

For citation: Drapkina O. M., Bubnova M. G., Samorodskaya I. V., Akulova O. A., Aronov D. M. Changes in mortality rates from acute types of coronary artery disease in Russia for the period from 2015 to 2019. *Russian Journal of Cardiology*. 2021;26(5):4441. (In Russ.) doi:10.15829/1560-4071-2021-4441

According to the World Health Organization (WHO), cardiovascular diseases (CVDs) are the first of the 10 leading causes of death in the world [1]. According to the Global Burden of Disease, in 2015, more than 400 million people worldwide suffered from CVD [2]. In the 2015, 17,7 million people died from CVD, which accounted for 31% of all deaths in the world [3]. The cause of death of 7,4 million people was coronary artery disease (CAD).

Over the past two decades, a decrease in the age-standardized mortality rate from CVD has been noted worldwide: from 393 to 286 deaths per 100 thousand population [2]. The highest mortality rate from CAD in the Russian Federation (RF) referred to the period 1995-1998 and was 330 and 154 per 100 thousand men and women, respectively [4]. Moreover, these values were similar to those for 1985-1989. According to the Federal State Statistics Service, there was 633 cardiovascular deaths per 100 thousand population in 2019, while a year earlier it was 622,1 deaths per 100 thousand population [5].

In the last decade, significant efforts have been made to reduce mortality from CVD in Russia. In this regard, it is necessary to assess the effectiveness of the measures taken and to study the CVD mortality rates not only at the national, but also at the regional levels. These analyzes are the basis for further creation of effective regional programs aimed at improving the quality and availability of health care, and reducing the mortality rate of the population.

The aim was to identify regional specifics of changes in mortality rates from acute types of CAD in 82 Russian regions for the period from 2015 to 2019.

Material and methods

The study used Federal State Statistics Service data on the average annual population and the death number in one-year age groups in 2015 and 2019 by 82 Russian regions using Brief nomenclature of causes of death of Rosstat (C41 and C51). The term "acute" myocardial infarction (MI) in this nomenclature corresponds to codes I21.0-9 in the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10), "subsequent" MI — codes I22.0-9, "other acute CAD types" — code I24.8. The study analyzed mortality rates from acute and subsequent MI, all cases of MI (sum of codes — I21-I22), other acute types and all acute types of CAD (sum of codes — I21-I22, I24.8). Standardized mortality ratio (SMR) was estimated using special software. Comparison of mortality was carried out based on SMR calculated according to the European Standard Population by direct standardization per 100 thousand population. Comparison of the regional mean SMR values in 2015 and 2019 for each of the death causes and their differences in SMR was performed using the nonparametric Wilcoxon test. The absolute and relative increase/ldecrease values, coefficient of variation (CV), maximum and minimum SMR and their ratio were estimated. Calculations and graphical data analysis were carried out using Statistica 6.0 and Microsoft Excel software packages.

Results

Dynamics in mortality from all acute CAD types

Table 1 shows mortality rates (per 100 thousand population), depending on the ICD-10 code, their dynamics and CV. During the period 2015-2019, average SMR from all acute CAD types decreased by 21% in Russia. At the same time, the absolute decline (per 100 thousand population) amounted to -17,3. The maximum SMR from all three acute CAD types per 100 thousand population in 2015 and 2019 were registered in the Krasnoyarsk Krai: 216,27 and 222,08, respectively (with a 3% increase), and the minimum — in the Republic of Dagestan: 13,77 and 12,49, respectively (with a 9% decrease) (Table 2). Over the period from 2015 to 2019, the CV increased by 6%, and the max/min ratio increased from 10,2 to 17,8.

The decrease in SMR from all three acute CAD types varied from -85% in the Chechen Republic (from 100,66 to 14,83 per 100 thousand population) to -1,0% in Arkhangelsk (from 66,94 to 65,96 per 100 thousand population) and Rostov (from 40,05 to 39,48 per 100 thousand population) regions. In 28 Russia subjects, the decrease in mortality from all acute CAD types was associated with a decrease in all SMR components — acute MI, subsequent MI and other acute CAD types.

An increase in mortality from all three acute CAD types from 2015 to 2019 was observed in 13 Russian regions. The most noticeable increase (+83%; from 61,73 to 113,09 per 100 thousand population) in mortality from all acute CAD types over 5 years occurred in the Chukotka Autonomous Okrug. In the only constituent entity of the Russian Federation — in the Kemerovo region, the increase in mortality from all forms of acute coronary artery disease (by 27%) was due to an increase in each of the SCS: from acute MI by 51%, subsequent MI by 14% and other acute CAD types by 13%.

Dynamics in mortality from all MI cases

In the Russian Federation, mortality from all cases of MI (acute and subsequent) for 5 years decreased by 14%. At the same time, the absolute decline was -4,13 per 100 thousand population. The analysis by regions showed a decrease in mortality from all MI cases over 5 years in 61 Russian regions.

Table 1

Mortality (SMR) per 100 thousand population from acute CAD types in 2015 and 2019 in Russia and their dynamics

Death cause	Code in ICD-10	SMR		Absolute increase/ decrease	% increase/ decrease	Coefficient of variation (CV)	
		2015г	2019г			2015г	2019г
All acute CAD types	I21-I22, I24.8	67,6	50,3	-17,3	-21	60%	66%
All MI cases (acute and subsequent)	I21-I22	36,5	30,8	-5,76	-14	46%	47%
Acute MI	I21.0-I21.9	26,8	23,6	-3,25	-9	44%	47%
Subsequent MI	I22.0-I22.9	9,7	7,2	-2,51	-22	69%	75%
Other acute CAD types	I24.8	31,0	19,5	-11,54	-21	103%	134%

Abbreviations: CAD — coronary artery disease, MI — myocardial infarction, ICD-10 — International Statistical Classification of Diseases and Related Health Problems, the tenth revision, SMR — standardized mortality ratio, CV — coefficient of variation.

Table 2

Maximum and minimum mortality (SMR) per 100 thousand population from acute CAD types in 2015 and 2019 in Russia

Death cause	Code in ICD-10	Highest SMR		Lowest SMR		Max//min ratio	
		2015г	2019г	2015г	2019г	2015г	2019г
All acute CAD types	I21-I22, I24.8	216,27	222,08	13,77	12,49	15,7	17,8
All MI cases (acute and subsequent)	I21-I22	107,90	100,71	5,10	6,41	21,16	15,7
Acute MI	I21.0-I21.9	79,08	76,84	3,69	6,41	21,43	11,99
Subsequent MI	I22.0-I22.9	34,54	23,88	1,05	0,00	32,9	-
Other acute CAD types	I24.8	144,43	169,16	2,37	0,74	60,94	228,59

Abbreviations: CAD — coronary artery disease, MI — myocardial infarction, ICD-10 — International Statistical Classification of Diseases and Related Health Problems, the tenth revision, SMR — standardized mortality ratio.

The largest decrease in all MI mortality from 2015 to 2019 was recorded in the Chechen (-78%) and Karachay-Cherkess (-52%) Republics, the Republic of Kalmykia (-54%), and the Volgograd region (-52%). More than a third of all MI decreased in St. Petersburg (-33%) and the Leningrad region (-36%), the Republic of Tatarstan (-47%), Buryatia (-33%) and Sakha (36%), Astrakhan (-47%), Tver (-37%), Ulyanovsk (-40%) and Murmansk (-34%) regions, and Primorsky Krai (-34%).

Only in 41 Russian regions, the five-year reduction in mortality from all MI cases was due to a simultaneous decrease in the SMR from acute and subsequent MI. At the same time, in 20 Russian regions, the decrease in mortality from all MI cases for 2015-2019 was due to the positive dynamics of only one of SMR components:

– from acute MI — in 9 Russian regions (with a SMR increase from subsequent MI): Kursk and Novgorod Oblasts, the Republics of Altai, Dagestan, Komi, Mari El, North Ossetia-Alania, Tyva, Udmurt;

– from subsequent MI — in 11 Russian regions (with a SMR increase from acute MI): in Belgorod, Kaliningrad, Kaluga, Kamchatka, Kurgan, Orenburg, Samara and Smolensk Oblasts, Kabardino-Balkar Republic, Perm Krai, Chukotka Autonomous Okrug.

The maximum SMR from all MI cases per 100 thousand population in 2015 and 2019 was registered in the Magadan region: 107,9 and 100,71, respectively (with a 7% decrease in mortality), and the minimum SMR — In the Republic of Ingushetia: 5,10 and 6,41, respectively (with a 26% increase in mortality).

By 2019, mortality from all MI cases increased in 20 Russian regions. The smallest increase (up to 1%) was in the Bryansk, Vladimir, Ivanovo, Kostroma, Lipetsk, Pskov and Yaroslavl Oblasts, as well as in the Republic of Karelia. The maximum growth in SCR was in Kemerovo (+12,13 per 100 thousand population, or +39%) and Jewish Autonomous (+11,63 per 100 thousand population, or +22%) Oblasts. An increase in mortality from all MI cases with a simultaneous increase in the SMR from acute

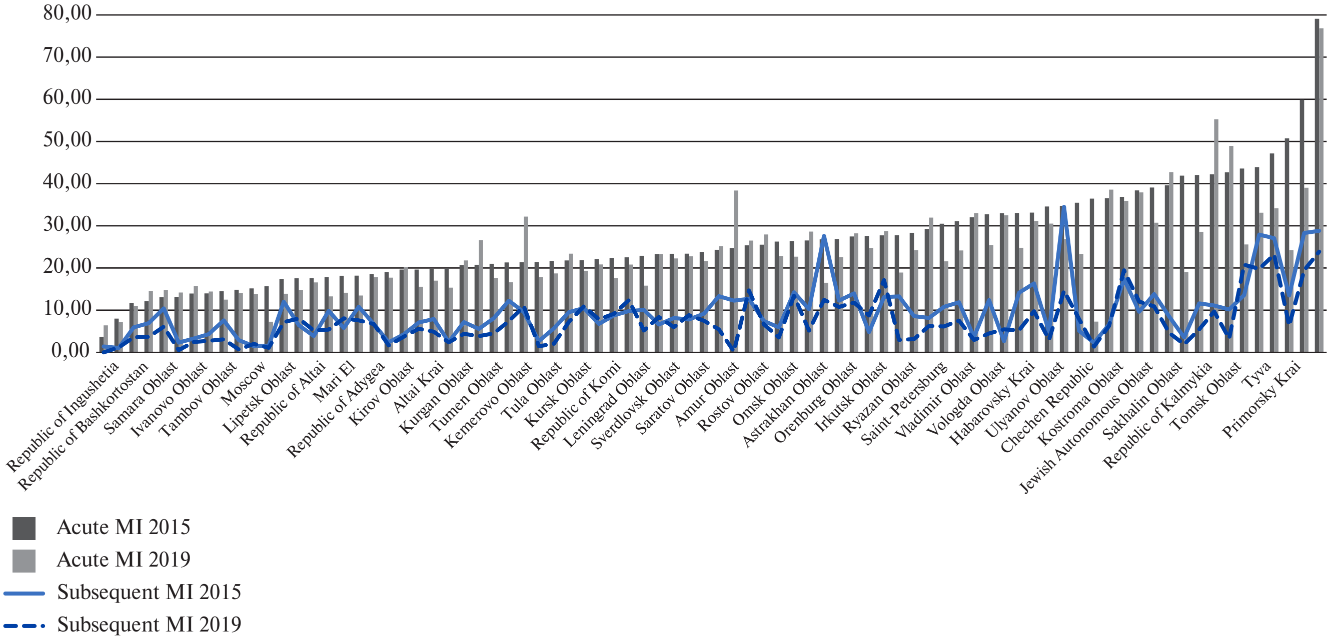

Figure 1 Standardized mortality ratio (per 100 thousand population) from all forms of acute coronary heart disease (I 21–I 22, I 24.8) and their fluctuations between the regions of the Russian Federation in 2015 and 2019.
Abbreviation: MI — myocardial infarction.

and subsequent MI was observed in Kemerovo (by 51% with acute MI and by 14% with subsequent MI), Irkutsk (by 4% and 31%, respectively) and Oryol (by 4% and 16%, respectively) Oblasts.

Mortality from all MI cases by 2019 increased due to acute MI in 11 Russian regions (Amur, Vladimir, Jewish Autonomous, Ivanovo, Novosibirsk, Pskov, Rostov and Yaroslavl Oblasts, Zabaykalsky Krai and the Republic of Ingushetia), and due to subsequent MI in 7 regions (Bryansk, Vologda, Kostroma and Lipetsk Oblasts, Republics of Karelia and Khakassia, Stavropol Krai).

Dynamics in mortality from acute and subsequent MI

Mortality from acute MI in Russia for the period 2015-2019 decreased by -3,25 per 100 thousand population (-9%) (Table 1). In 56 Russian regions in 2019, a decrease in the SMR from acute MI was recorded in the range from -1% to -80% compared to 2015. With a twofold decrease in the max/min ratio (from 21,43 to 11,99), the CV increased by 3% over a five-year period.

The largest decrease in the SMR from acute MI per 100 thousand population from 2015 to 2019 was recorded in the Chechen Republic (-29,15). The highest mortality rates from acute MI both in 2015 and in 2019 were recorded in the Magadan Oblast (79,08 and 76,84, respectively, per 100 thousand population), and the lowest in the Republic of Ingushetia (3,69 and 6,41, respectively, per 100 thousand population). The subjects with the lowest mortality rate from acute MI in 2019 were as follows: Republics of Dagestan (7,14) and Altai (14,13), Karachay-Cherkess (7,28) and Chechen (7,30) Republics, Moscow (12, 52) and the Tambov Oblast (13,91).

The decrease in mortality from subsequent MI by 2019 relative to 2015 was -2,51 per 100 thousand population (-22%) (Table 1). The largest decrease in SMR from subsequent MI (-19,93 per 100 thousand population) by 2019 was recorded in the Ulyanovsk Oblast. At the same time, the highest mortality rate from subsequent MI (23,88 per 100 thousand population) in 2019 was recorded in the Magadan Oblast (and in 2015 in the Ulyanovsk Oblast — 34,51 per 100 thousand population).

There were no deaths from subsequent MI in 2019 in the Republic of Ingushetia (in 2015, the SMR was 1,42). The lowest mortality rate from subsequent MI in 2019 was recorded in the Amur Oblast (0,22 per 100 thousand population). In 2019, the SMR from subsequent MI were low in 10 Russian regions: Kabardino-Balkarian (0,55), Karachay-Cherkess (1,08) and Chechen (1,37) Republics, Republics of Mordovia (0,70), Crimea (1,46), Kalmykia (1,90) and Mari El (2,00), Sevastopol (1,64), Tula (2,04) and Belgorod (2,73) Oblasts.

Dynamics in mortality from other acute CAD types

The decrease in mortality from other acute CAD types for the period from 2015 to 2019 amounted to -11,54 (21%). Attention is drawn to the higher CV (103% in 2015 and 134% in 2019; a 31% increase) and a sharp increase in the max/min ratio (from 60,94 to 228,53, respectively).

The maximum SMR from other acute CAD types both in 2015 and in 2019 was recorded in the Krasnoyarsk Krai (144,43 and 169,16, respectively, per 100 thousand population), and the minimum SMR — in 2015 in the Tula Oblast (2,37 per 100 thousand population) and in 2019 — In the Astrakhan Oblast (0,74 per 100 thousand population).

Mortality from other acute CAD types in Russian regions varied over a five-year period: from a decrease in the Oryol Oblast (-92%; from 116,52 to 9,6 per 100 thousand population) to an almost sevenfold increase in the Chukotka Autonomous Okrug (+51,95%; from 8,9 in 2015 to 60,85 in 2019 per 100 thousand population).

Discussion

The results obtained reveal significant differences in SMR between the regions, which require additional discussion (Figure 1). The left diagram wing reflects the low and moderate mortality from all acute CAD types, mainly in the Central and Southwestern Russia, and the right wing is, for the most part, Siberian, Northern and Far Eastern regions with higher SMR values. Similar geographic imbalances exist in almost all countries. Statistics show that rural residents use ambulance services almost 2 times less often than urban residents (6,4% vs 10,3%), and higher mortality are recorded in regions with vast territories and remote rural settlements [6]. And, from our point of view, this problem requires further study.

In general, the decrease in mortality from acute CAD types by 2019 was formed due to the decrease in SMR from all three types in 69 Russian regions, from all MI cases (acute and subsequent) — in 61 subjects, from acute MI — in 58 subjects, from subsequent MI — in 62 subjects, and from other acute CAD types — in 61 subjects. At the same time, the decrease in the SMR from all acute CAD types due to a simultaneous decrease in each acute CAD type (acute and subsequent MI, other acute CAD types), indicating a real decrease in mortality, developed only in 28 regions.

Among the subjects with a unidirectional positive trend, the Sakhalin Oblast showed the maximum degression. The highest (more than 2-fold) rate of SMR decrease for three CAD types was noted in the Karachay-Cherkess Republic (by 55%), the Tver Oblast (by 59%), and the Chechen Republic (by 85%). In other subjects, there is a multidirectional dynamics in mortality rates for acute MI, subsequent MI and other acute CAD types, probably due to both objective and subjective factors.

One of these factors is a methodologically different approach to determining the initial death cause and incorrect accounting of death causes. In Russia, there are certain problems with the interpretation of the terms of acute CAD types, diagnosis and coding them in statistical documents, which can affect mortality rates [7].

The last 2 years, work has been carried out to adapt the Russian clinical classification of CAD to the requirements and terminology of ICD-10. Methodological and practical difficulties consisted in the fact that according to ICD-10, MI is considered to be "subsequent" if it develops within 4 weeks from onset of a previous infarction. All other cases of acute MI are included in I21.0-0, regardless of whether it is the first, second, or third, and are classified as "acute MI". Thus, ICD-10 do not divide cases of acute MI into "first", "second", etc. WHO has now removed subsequent MI (I22) from mortality statistics, instead using I21. However, according to the Brief nomenclature of causes of death of Rosstat, the I22 code continues to be accounted for as a separate line.

This is probably due to the fact that in Russia, "subsequent MI" is considered as MI that developed 28 days after the primary MI, which is coded as I22, which led to the division of MI into "primary" and " subsequent " (ie, second, third, etc.). The rationale for this approach is that patients with subsequent MI have a worse prognosis and, accordingly, require other rehabilitation measures, secondary prevention and medical examination. In the 2020 Russian Guidelines on clinical, morphological and statistical classification of coronary artery disease, it is recommended:

1) to consider the term "acute" to be statistical and include it in diagnosis for subsequent unambiguous interpretation of the diagnosis as I21;

2) to save the term "subsequent MI" with coding I22;

3) in case of MI within 4 weeks from onset of a previous infarction, to register it as "Recurrent MI [8].

Thus, at present, differences in approaches to terminology and coding remain between the ICD-10 and Russian Society of Cardiology. These differences affect the variability of regional indicators and their dynamics.

The all-Russian trend of a decrease in mortality from MI, which has a multidirectional nature, testifies only to a partial success and once again exposes the coding defects, as well as, probably, the problems of providing health care in a number of regions. It is believed that the mortality rate from primary MI to a greater extent reflects the situation with the inpatient care for this disease, and the mortality rate from subsequent MI — with the provision of outpatient care [7]. However, this hypothesis requires further confirmation.

Significant fluctuations of regional SMR are characterized by CV and the max/min ratio. The CV <33% indicates the relative homogeneity of the studied population, and the CV >66% revealed in our analysis most likely confirm the problems with coding the death causes and, probably, indicate an asymmetric care in the regions (Table 1).

From our point of view, the unidirectional changes in all three acute CAD types most clearly reflects the situation in regions, and the multidirectional changes is due to difficulties in coding, diagnosis, treatment and secondary prevention in each specific region. But the growth in mortality rates, as well as the multidirectional dynamics, requires identifying the reasons for such changes in each specific area.

Conclusion

In 2019, compared to 2015, a decrease in mortality from acute CAD types was recorded in most Russian regions. The identified regional specifics require clarification of approaches to death cause coding and the introduction of additions to mortality reduction programs, taking into account the specifics of each Russian region.

Relationships and Activities: none.

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